NEUROTRAUMA 2015

The 33rd Annual Symposium of the

National Neurotrauma Society

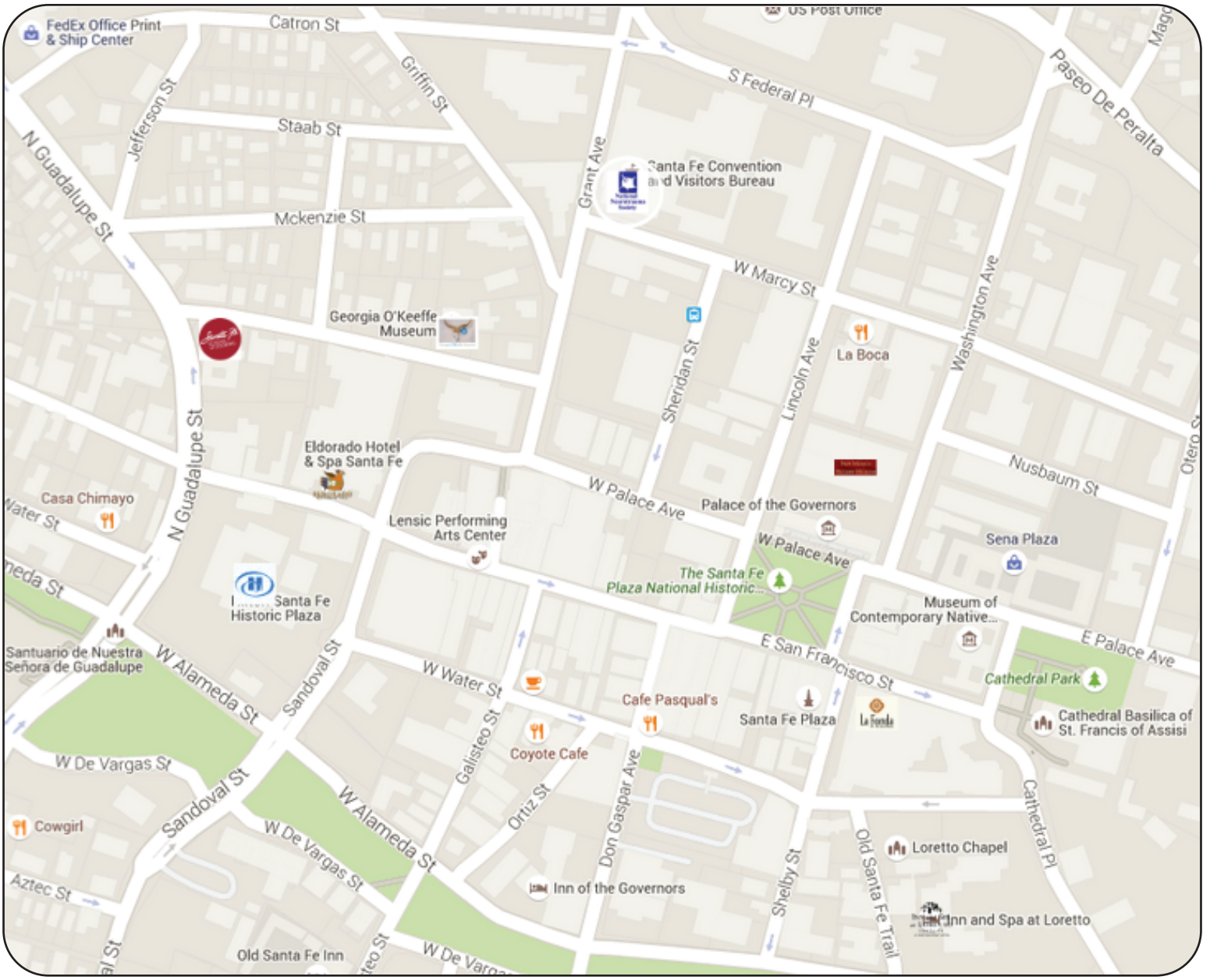
SCIENTIFIC PROGRAM

June 28 - July 1

Santa Fe, New Mexico

WWW.NEUROTRAUMA.ORG

DOWNTOWN SANTA FE MAP



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National Neurotrauma Society

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Letter from the President

Dear Neurotrauma Colleagues:

On behalf of the National Neurotrauma Society, I would like to welcome you to Santa Fe, New Mexico for the 33rd Annual Symposium of the National Neurotrauma Society. This symposium has been the primary forum for exchanging information in the fields of both traumatic brain and spinal cord injury for many years. The meeting focuses on integrating clinical, translational and basic science information on issues in neurotrauma.

This year's meeting, co-hosted by the National Neurotrauma Society and the AANS/CNS Joint Section on Neurotrauma and Critical Care, will present an exciting integration of state-of-the-art clinical, translational and basic science information on the consequences of damage to the nervous system. This years' meeting, whose theme is "Understanding CNS Injury—Are We Still in the Wild West?", will have informative discovery, translational, and clinical sessions and a workshop, as well as programs for students and early career investigators. These focus on topics of current research and practice issues. Patient perspective talks and networking opportunities will round out the program. CME credits will be provided for each day of the meeting.

The four host hotels are in the heart of old town, close to museums, short walks to many and varied restaurants, shops, and Canyon Road. Our two social events include an opening welcome reception and an evening at the New Mexico History Museum. There will also be time for you to enjoy the city as well whether it is at lunch or in the evening.

No other conference combines basic science, preclinical modeling and clinical approaches to studying brain and spinal cord injury to the extent that is done at this meeting. We look forward to an exciting and productive few days. On behalf of the members of the Program Committee, along with the officers, councilors and members of the National Neurotrauma Society, we welcome you to Santa Fe, and hope that you have an enjoyable and educational meeting!

Sincerely,

Helen Bramlett, Ph.D.
President, National Neurotrauma Society
NNS 2015 Scientific Program Chair

Neurotrauma 2015 Supporters

The National Neurotrauma Society gratefully acknowledges receiving generous support from the following sponsors:

PLATINUM ($10,000+)

THE MIAMI PROJECT TO CURE PARALYSIS

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

NATIONAL INSTITUTES OF HEALTH

Grant # 1R13NS093845-01

American Association of Neurological Surgeons

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Better surgery for a better world

ISN International Society for Neurochemistry

Exhibitors

AANS/CNS Section on Neurotrauma & Critical Care [17]
www.neurotraumasection.org
The purpose of the AANS/CNS Section is to provide a forum for education and research on trauma and critical care of the nervous system, to coordinate activities and programs relating to trauma, critical care and sports medicine for the parent organizations and other societies, committees and agencies, to represent the parent organizations, at their discretion, at any organization or group on matters relating to trauma, critical care and sports medicine, to advise the parent organizations of activities which relate to nervous system trauma and critical care by other individuals, group and/or agencies.

Baylor Scott & White Health [19]
www.sw.org
The largest not-for-profit health care system in Texas, Baylor Scott & White Health was born from the 2013 combination of Baylor Health Care System and Scott & White Health. Known for exceptional patient care for more than a century, Baylor Scott & White Health includes 49 hospitals, more than 500 patient care sites, 5,800 affiliated physicians and 35,000 employees as well as the Scott & White health plan.

Centre for Neuro Skills [10]
www.neuroskills.com
Since 1980, Centre for Neuro Skills (CNS) has delivered postacute medical treatment, therapeutic rehabilitation and disease management services with specially-trained staff for individuals recovering from acquired brain injury . Our cost-effective, patient-centered programs maximize treatment effect, learning generalization and stability of recovery in real-world settings. The goal: to facilitate skill acquisition and help each patient resume a normal rhythm of living.

Codman Neuro [6] and Depuy Synthes [7]
www.depuysynthes.com
At the DePuy Synthes Companies, we listen to the moving stories of patients experiencing orthopaedic and neurological conditions and to the healthcare professionals who treat them. Then we deliver total solutions to help people live full lives.

Defense & Veterans Brain Injury Center [22]
http://dvbic.dcoe.mil
DVBIC, the traumatic brain injury operational component of the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury, serves active duty military, their beneficiaries, and veterans with traumatic brain injuries through innovative clinical research initiatives, state-of-the-art clinical care, and educational programs.

Ethicon [4]
www.ethicon.com
At Ethicon, we are committed to advancing surgical care worldwide to enhance patients' lives. By working together, we can find solutions to expand access to quality care globally. Our solutions must provide every customer not only the best product offerings, but the best value and service.

Federal Interagency Traumatic Brain Injury Research (FITBIR) [14]
fitbir.nih.gov
The Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system was developed to share data across the entire TBI research field and to facilitate collaboration between laboratories, as well as interconnectivity with other informatics platforms.

Hemedex [2]
www.hemedex.com
Hemedex's technology provides early warning of tissue ischemia, helps target therapy, monitors real-time response to intervention, and provides prognostic information. Hemedex provides a complete solution for continuous, real-time measurement of cerebral perfusion in absolute units by offering the Bowman Perfusion Monitor, perfusion probe, titanium bolts and cranial drill bits.

Hocoma [9]
www.hocoma.com
Hocoma is the global market leader for the development, manufacturing and marketing of robotic and sensorbased devices for functional movement therapy. We are a globally active medical technology company based near Zurich, Switzerland. We develop innovative therapy solutions working closely with leading clinics and research centers.

Integra LifeSciences [1]
www.integralife.com
Integra LifeSciences, a world leader in medical technology, is dedicated to limiting uncertainty for surgeons, so they can concentrate on providing the best patient care. Integra offers innovative solutions in orthopedic extremity surgery, neurosurgery, spine surgery, and reconstructive and general surgery.

Journal of Neurotrauma [29]
www.liebertpub.com/neu
The Journal of Neurotrauma is the official journal for NNS and the flagship, peer-reviewed publication for reporting on the latest advances in both the clinical and laboratory investigation of traumatic brain and spinal cord injury. Membership in NNS provides you with an online subscription with immediate access to the Journal's fully searchable archival content of over 31 years.

K2M Group Holdings, Inc. [15]
www.k2m.com
K2M Group Holdings, Inc. is a global medical device company focused on designing, developing and commercializing innovative complex spine and minimally invasive spine technologies and techniques used by spine surgeons to treat some of the most difficult and challenging spinal pathologies. K2M has leveraged these core competencies to bring to market an increasing number of products for patients suffering from degenerative spinal conditions. These technologies and techniques, in combination with a robust product pipeline, enables the company to favorably compete in the global spinal surgery market.

Leica Biosystems [8]
www.leicabiosystems.com
Leica Biosystems, a global leader in workflow solutions and automation, provides anatomical pathology laboratories and researchers a comprehensive product range for each step in the pathology process, from sample preparation and staining to imaging and reporting. Our easy-to-use and consistently reliable offerings help improve workflow efficiency and diagnostic confidence.

Moberg Research [24]
www.moberg.com
The mission of Moberg Research is to develop an integrated, patient-centric, information environment to improve patient safety and optimize care. Our focus application area is in the urgent, acute, and surgical care of neurological patients such as head trauma, stroke, aneurysms, and related disorders.

National Neurotrauma Society [30a]
www.neurotrauma.org
The National Neurotrauma Society is committed to the promotion of neurotrauma research by enhancing communications, providing a forum, and increasing support on the national and international level. The National Neurotrauma Society seeks to accelerate research that will provide answers for clinicians and ultimately improve the treatments available to patients.

Neuroscience Associates Inc. [3]
www.nsalabs.com
Proprietary MultiBrain® and MultiCord® technologies enable simultaneous sectioning and staining of up to 40 neuronal tissues, achieving uniform processing across treatment groups. Coupling mass production neurohistology with staining expertise including standard stains, immunohistochemistry and specialty stains for disintegrative degeneration and Alzheimer's pathology, NeuroScience Associates significantly reduces client's R&D cycle times.

One Mind [29]
www.onemind.org
One Mind is a non-profit organization dedicated to benefiting all affected by brain illness and injury through fostering fundamental changes that will radically accelerate the development and implementation of improved diagnostics, treatments and cures — while eliminating the stigma that comes with mental illness. Our mission is fueled by our belief in open science principles and creating global public-private partnerships among governmental, corporate, scientific and philanthropic communities.

Oxyhealth LLC [20/21]
www.oxyhealth.com
At OxyHealth, our mission is to ethically deliver chambers to doctors, who know the science they are prescribing to patients, who actually need this product. Quite simply, OxyHealth wants to provide hyperbaric chambers to those who have been examined, diagnosed, and deemed to need our chambers—to those patients who will gain from a physician's hands-on protocol and expertise.

Penn Center for Brain Injury & Repair [13]
www.med.upenn.edu/cbir
Over 25 principal investigators and their research personnel form the Penn Center for Brain Injury and Repair. Working in a highly collaborative environment, these researchers are studying ways to significantly improve the quality of life for people suffering from traumatic brain injury (TBI) and to prevent the "secondary" or delayed injuries that are initiated by brain trauma.

QuesGen Systems, Inc. [26]
www.quesgen.com
QuesGen Systems is a web-based CTMS (Clinical Trial Management System) developed for academic and commercial research studies and clinical trials with a particular focus and expertise in the area of data management for TBI Research. The QuesGen platform is not only HIPAA compliant but is also CFR 21 Part 11 certified. QuesGen offers application management of all information from recruiting and screening of prospective participants, tracking and collecting all data during the execution of the study and provides tools that allow easy extract into leading statistical packages.

Raumedic [23]
www.raumedic.com
Raumedic supplies precision neuromonitoring products for rapid, safe and accurate ICP, temperature and oxygen partial pressure measurements. NEUROVENT-PTO integrates ICP, temperature and oxygen partial pressure into 1 catheter, with no catheter calibration or refrigeration necessary. NEUROVENT ventricular ICP catheters can simultaneously drain CSF and monitor ICP and temperature.

SC Medical Books / Elsevier [27]
http://www.us.elsevierhealth.com/
Finest quality medical publications.

Siemens Healthcare [18]
www.usa.healthcare.siemens.com
Siemens Healthcare, Imaging and Therapy Divisions provide advanced imaging in the core neuro specialties of Computed Tomography, Neuro Interventional/Neuro Surgery and Magnetic Resonance.

University of California BIRC [25]
http://neurosurgery.ucla.edu
The faculty members of UCLA Neurosurgery are committed to providing the finest and most comprehensive patient care through innovative clinical programs in minimally invasive brain and spinal surgery, neuroendoscopy, neuro-oncology for both adult and pediatric brain tumors, cerebrovascular surgery, stereotactic radiosurgery for brain and spinal disorders, surgery for movement disorders such as Parkinson's disease, and epilepsy surgery.

University of Kentucky [11]
www.mc.uky.edu/scobirc
The Spinal Cord and Brain Injury Research Center (SCoBIRC) at the University of Kentucky College of Medicine was established in 1999 to promote both individual and collaborative studies on injuries to the spinal cord and brain that result in paralysis or other loss of neurologic function.

VisitLEX / Lexington CVB [12]
www.visitlex.com
Lexington, Kentucky showcases all Kentucky's charm, natural beauty and Southern hospitality with elegance and sophistication. We've distilled all the best Kentucky has to offer in one charming but cosmopolitan city. Visit our booth to learn more about the site of Neurotrauma 2016!

Women in Neurotrauma Research [30b]
www.nationalneurotraumasociety.org/wintr
WiNTR is an organization established to promote international gender equality in neurotrauma research. WINTR is an organization for all individuals interested in these aims, regardless of gender. We appreciate a wide diversity of ideas and opinions to help the organization successfully meet its goals. The mission of WiNTR is to promote gender equality through mentoring and networking activities.

ZOLL Medical Corporation [7]
www.zoll.com
ZOLL Medical Corporation, a leader in medical products and software solutions, offers Intravascular Temperature Management (IVTM™) solutions, which provide healthcare professionals with the power and control needed to rapidly, safely, and more effectively manage the core body temperature of critically ill or surgical patients with warming and cooling applications.

Invited Faculty Speakers & Chairs

NAME	UNIVERSITY	SESSION	DAY	ROLE
Denes Agoston, MD, PhD	Uniformed Services University	PL07	WED	Speaker & Session Chair
Kim Anderson-Erisman, PhD	University of Miami	S02	MON	Session Chair
		PL04	TUES	Session Chair
Esperanza Arias Perez, PharmD, PhD	Einstein University	PL06	WED	Speaker
Vishal Bansal, MD	University of California, San Diego	S13	TUES	Speaker
William Barr, PhD	New York University	PL03	TUES	Speaker
D. Michele Basso, EdD	Ohio State University	S09	TUES	Speaker & Session Chair
Larry Benowitz, PhD	Boston Chiidren's Hospital, Harvard University	PL06	WED	Speaker
Detlev Boison, PhD	Legacy Research Institute, Dow Neurobio Labs	S14	TUES	Speaker
Corina Bondi, PhD	University of Pittsburgh	PL03	TUES	Speaker & Session Chair
Cesar Borlongan, PhD	University of South Florida	S01	MON	Speaker
Helen Bramlett, PhD	University of Miami	PRES	ALL	Program Chair
Robert Brownstone, MD, PhD	Dalhousie University	S06	MON	Speaker
Mark Burns, PhD	Georgetown University	S05	WED	Speaker & Session Chair
Susan Charlifue, PhD	Craig Hospital	S02	MON	Speaker
Dawn Comstock, PhD	University of Colorado, Denver	S07	TUES	Speaker
Rachel Cowan, PhD	University of Miami	S02	MON	Speaker
Charles Cox, Jr., MD	University of Texas	S04	MON	Speaker & Session Chair
Fiona Crawford, PhD	Roskamp Institute	S05	MON	Speaker
Pramod Dash, PhD	University of Texas	S04	MON	Speaker
Sanjay Dhall, MD	University of California, San Francisco	AANS 1	SUN	Speaker
Ramon Diaz-Arrastia, MD, PhD	Uniformed Services University	S03	MON	Speaker
Dara Dickstein, PhD	Mt. Sinai Hospital	PL05	TUES	Speaker
W. Dalton Dietrich, PhD	University of Miami	PL02	MON	Speaker & Session Chair
Ann-Christine Duhaime, MD	Harvard University	AANS 4	SUN	Speaker
Timothy Duong, PhD	University of Texas San Antonio	S03	MON	Speaker & Session Chair
Linda Ewing-Cobbs, PhD	University of Texas Health Science Center	S04	MON	Speaker & Session Chair
Sam Gandy, MD, PhD	Mt. Sinai Hospital	PL05	WED	Session Chair
Aruna Ganju, MD	Northwestern University	AANS 3	SUN	Speaker
Gerard Gioia, PhD	Children's National Medical Center	S07	TUES	Speaker
Christopher Giza, MD	University of California Los Angeles	S07	TUES	Session Chair
Jonathan Godbout, PhD	Ohio State University	S09	TUES	Speaker
Grace Griesbach, PhD	Centre for NeuroSkills	S09	TUES	Speaker
Kevin Guskiewicz, PhD	University of North Carolina	S07	TUES	Speaker
Jennifer Hay	University of Glasgow	WLW	MON	Speaker
Michal Hetman, MD, PhD	University of Louisville	PL06	WED	Session Chair
Ramona Hicks, PhD	One Mind	S10	TUES	Session Chair
Gregory Holmes, PhD	Penn State University	PL01	MON	Session Chair
Jason Huang, MD	Baylor Scott & White Health	AANS 1	SUN	Speaker
Edwin Jackson, PhD	University of Pittsburgh	S14	TUES	Speaker
Travis Jackson, PhD	University of Pittsburgh	PL01	MON	Speaker
Victoria E. Johnson, PhD	University of Pennsylvania	WLW	MON	Speaker
Barry Jordan, MD	Burke Rehabilitation Hospital	S05	MON	Session Chair
		PL05	TUES	Speaker
Jenifer Juranek, PhD	University of Texas	S04	MON	Speaker
Sujatha Kannan, MD	Johns Hopkins University	S01	MON	Speaker
Gregory Kapinos, MD	Hofstra University	AANS 2	SUN	Speaker
Anthony Kline, PhD	University of Pittsburgh	PL03	TUES	Session Chair
Patrick Kochanek, MD	University of Pittsburgh	S08	TUES	Speaker
		S14	WED	Session Chair
Shekar Kurpad, MD	Medical College of Wisconsin	AANS 3	SUN	Session Chair
Michael Lane, PhD	Drexel University	PL01	MON	Speaker

Invited Faculty Speakers & Chairs

NAME	UNIVERSITY	SESSION	DAY	ROLE
Michelle LaPlaca, PhD	Georgia Institute of Technology/Emory University	S07	TUES	Session Chair
Vance Lemmon, PhD	University of Miami	PL07	WED	Speaker
Allan Levi, MD, PhD	University of Miami	AANS 3	SUN	Speaker
		PL02	MON	Speaker
Jonathan Lifshitz, PhD	University of Arizona	S13	WED	Session Chair
Cathy Liu, MD	University of California, Davis	PL04	TUES	Speaker
Bruce Lyeth, PhD	University of California, Davis	S12	TUES	Session Chair
David Magnuson, PhD	University of Louisville	S06	MON	Speaker
Christina Master, MD	CHOP/University of Pennsylvania	AANS 4	SUN	Speaker
Andrew Mayer, PhD	The Mind Research Network	S03	MON	Speaker
Mary Ellen Michel, PhD	National Institutes of Health	WNR	MON	Speaker
Stefania Mondello, MD, PhD	University of Messina	S08	TUES	Speaker
Andre Obenaus, PhD	Loma Linda University	S03	MON	Session Chair
David Okonkwo, MD, PhD	University of Pittsburgh	PL02	MON	Speaker
Monica Perez, PT, PhD	University of Miami	PL01	MON	Speaker
Daniel Perl, MD	Uniformed Services University	AANS 4	SUN	Speaker
Phillip Popovich, PhD	Ohio State University	S11	TUES	Session Chair
		S13	WED	Speaker
Enrico Rejc, PhD	University of Louisville	AANS 3	SUN	Speaker
Courtney Robertson, MD	Johns Hopkins University	S01	MON	Session Chair
Richard Rodgers, MD	Goodman Campbell	AANS 1	SUN	Session Chair
Susanna Rosi, PhD	University of California, San Francisco	S01	MON	Session Chair
Uzma Samadani, MD, PhD	New York University	AANS 4	SUN	Session Chair
Sujata Saraswat, PhD	University of Louisville	PL06	WED	Speaker
Michael Schwarzschild, MD, PhD	Harvard University	S14	WED	Speaker
Bridgette Semple, PhD	University of Melbourne	S15	WED	Speaker & Session Chair
Kiarash Shahlaie, MD, PhD	University of California, Davis	PL04	TUES	Speaker
Lee Shapiro, MD	Texas A&M University	S13	WED	Speaker
Deborah Shear, PhD	Walter Reed Army Institute of Research	S08	TUES	Speaker
Thomas Sick, PhD	University of Miami	S15	WED	Speaker
Soren Singel, MD	Baylor Scott & White Health	AANS 2	SUN	Speaker
William Smith, MD, PhD	University Medical Center	AANS 1	SUN	Speaker
Douglas H. Smith, MD	University of Pennsylvania	PL07	WED	Speaker
Diane Snow, PhD	University of Kentucky	PL01	MON	Session Chair
William Stewart, PhD	University of Glasgow	WLW	MON	Speaker & Session Chair
Martina Stippler, MD	Harvard University	AANS 2	SUN	Speaker
James Stone, MD, PhD	University of Virginia	PL05	WED	Speaker
Emily Swartz-Besecker, PhD	Gettysburg College	S13	WED	Session Chair
Aya Takeoka, PhD	University of Basel	S06	MON	Speaker
Wolfram Tetzlaff, MD, PhD	University of British Columbia, ICORD	PL07	WED	Speaker
Christine Thomas, PhD	University of Miami	S02	MON	Speaker
Frank Tortella, PhD	Walter Reed Army Institute of Research	S08	TUES	Session Chair
Jamie Ullman, MD	North Shore University Hospital	AANS 2	SUN	Session Chair
Mike Vitek, PhD	Duke University	S05	MON	Speaker
Cole Vonder Haar, PhD	University of British Columbia	PL03	TUES	Speaker
Amy Wagner, MD	University of Pittsburgh	S15	WED	Speaker
Briana Walker-Tavano	Briana Walker International, Inc.	PL04	TUES	Speaker
Patricia Washington, PhD	Georgetown University	WLW	MON	Session Chair
Scott Whittemore, PhD	University of Louisville	S06	MON	Session Chair
		PL06	WED	Session Chair
Catharine Winstanley, PhD	University of British Columbia	S01	MON	Speaker

GENERAL INFORMATION

Registration Desk

The NNS 2015 Registration & Information Desk is located in the Main Lobby of the Santa Fe Convention Center. Visit during these hours to pick up your name badge, reprint a lost badge, ask general questions or add a ticketed event (on a space available basis).

SUNDAY, JUNE 28	7:00am-6:00pm
MONDAY, JUNE 29	7:00am-6:00pm
TUESDAY, JUNE 30	7:00am-6:00pm
WEDNESDAY, JULY 1	7:00am-4:00pm

Included Meals & Lunch Tickets

Registration for Neurotrauma includes the Welcome Reception on Sunday, daily breakfasts, coffee breaks and wine & cheese poster receptions.

With the exception of the the WiNTR Lunch Session on Monday and the Student/Post Doc lunch on Wednesday, all lunches are on your own. Tickets for these lunches were sold in advance when you registered for the conference. Onsite requests to add lunch tickets are on a space available basis only and cannot be guaranteed. *If you pre-ordered a lunch ticket and can no longer attend, please visit the Registration Desk.*

All pre-purchased event tickets are included in your name badge envelope.

Networking & Social Events

SUNDAY	
Welcome Reception	*Included for all attendees*
MONDAY	
WiNTR Lunch Session	*Lunch ticket $20, pre-order*
Wine & Cheese Poster Reception	*Included for all attendees*
WiNTR Mentoring Reception	*Tickets $25/$15 students*
TUESDAY	
Wine & Cheese Poster Reception	*Included for all attendees*
Land of Enchantment Evening	*Tickets $25/$15 students*
WEDNESDAY	
Awards Ceremony	*Included for all attendees*
Student/Post Doc Lunch	*FREE, advance RSVP only*

Tickets for these events were sold in advance when you registered for the conference. Onsite requests to add networking or social event tickets are on a space available basis only and cannot be guaranteed. *If you would like to purchase a ticket or if you pre-ordered a ticket and can no longer attend, please visit the Registration Desk.*

Exhibit Hours

All exhibits are located in Sweeney A-D Ballroom at the Santa Fe Convention Center.

SUNDAY, JUNE 28	10:00am-1:00pm
MONDAY, JUNE 30	7:00am-10:30am; 3:00pm-6:00pm
TUESDAY, JULY 1	7:00am-10:30am; 3:00pm-6:00pm

iWatch Drawing

Have your Exhibitor card signed at 10 or more exhibit booths and return it to the Registration Desk by 11:00 am on Wednesday to be eligible to win an iWatch. The drawing will be held during the Awards Ceremony on Wednesday morning. You must be present to win.

Educational Learning Objectives

At the conclusion of this three day symposium, attendees will be able to:

I. Describe injury models and novel approaches to study traumatic brain and spinal cord injury.

II. Identify advances in therapeutic targeting to enhance outcome after central nervous system injury.

III. Discuss controversial issues in the translation of therapeutic treatments from the laboratory to the clinic.

Post-Conference Evaluation Survey

All attendees will receive an overall survey via email on July 2. Your feedback helps us evaluate and improve the program for future years. Please be sure to complete this brief 5 minute survey. No code needed.

Future Meetings

Call for Proposals for Neurotrauma 2016

On August 1, 2015, all NNS members will receive an email invitation to submit proposals for scientific sessions for Neurotrauma 2016. Proposals will be reviewed by the 2016 Program Committee and combined with suggestions taken from the overall evaluation survey results to determine the program for next years' meeting.

NNS 2016 Proposal Deadline: September 15, 2015
Abstract Deadline: April 1, 2016

Download the NNS 2015 Mobile App

The Neurotrauma 2015 mobile app is available for download from iTunes and the Google Play store. The mobile app features include basic event information, venue maps, the ability to build a personalized agenda. You will be able to search all abstracts and speakers, take notes and receive push messages from the conference organizer so you remain up-to-date on all of the latest information.

SCHEDULE-AT-A-GLANCE

SUNDAY, JUNE 28

7:00 am- 6:00 pm **REGISTRATION DESK OPEN** *Santa Fe Convention Center Main Lobby*

7:45 - 8:45 **CNTA Breakfast** *La Fonda*

8:00 - 12:00
Chinese Neurotrauma Association Meeting
New Mexico Room @ La Fonda

Starting at 1:00 pm
Poster Mounting (Groups A & B)
Sweeney A-D @ SFCC

1:30 - 3:00
JNT Editorial Board Meeting
New Mexico Room @ La Fonda

03:00 - 4:30
WiNTR Business Meeting
Santa Fe Room @ La Fonda

4:30 - 6:00
NNS Officers & Councilors Meeting
Stiha Room @ LaFonda

7:00 - 8:30
Welcome Reception
La Terazza Rooftop Patio @ La Fonda

7:30 - 8:30 **AANS Breakfast** *SFCC*

8:30 - 12:00
AANS/CNS Sessions I & II *O'Keeffe Room @ SFCC*

BREAK

1:00 - 4:00
AANS/CNS Sessions III & IV *O'Keeffe Room @ SFCC*

MONDAY, JUNE 29 - *All sessions at SFCC*

7:00 am- 6:00 pm **REGISTRATION DESK OPEN** *Santa Fe Convention Center Main Lobby*

7:00 - 7:45
Poster Session I:
Groups A1-A4
Sweeney A-D

Breakfast & Exhibits
Sweeney A-D

PRESIDENT'S WELCOME

8:00 - 9:15
PL01
New Investigators & New Visions for CNS Injury Research
Sweeney E-F

9:15 - 10:30
S01
Clinically Relevant Models of Neuro-inflammation After TBI
Sweeney E-F

S02
Age & SCI
O'Keeffe

S03
Novel & Emerging Imaging for Detction & Diagnosis of TBI
Coronado

COFFEE BREAK

11:00 - 12:15
S04
Progenitor Cell Therapy for Adult TBI
Sweeney E-F

S05
The Role of apoE & APOE Genotype in Outcome after TBI
Coronado

S06
Genetic Dissection of Locomotor Circuitry
O'Keeffe

12:15 - 1:45
WiNTR Lunch Session
Human TBI Neuropathology
Peralta Room
ticket required

FREE TIME LUNCH ON YOUR OWN
All other attendees

1:45- 3:00
PL02
Therapeutic Hypothermia & Targeted Temperature Management After SCI & TBI: Is the Verdict Still Out?
Sweeney E-F

3:00 - 4:00
Poster Session II:
Groups A5-A8
Sweeney A-D

"Sweet Treat" Coffee Break & Exhibits

4:00 - 5:00
Poster Session III:
Groups B1-B4
Sweeney A-D

5:00 - 6:00
Poster Session IV:
Groups B5-B7
Sweeney A-D

Wine & Cheese & Exhibits

After 6:00
Poster Removal (Groups A & B)
Poster Mounting (Groups C&D)

6:00 - 8:00
WiNTR Mentoring & Networking Reception
Georgia O'Keeffe Museum

ticket required

TUESDAY, JUNE 30 - *All sessions at SFCC*

7:00 am- 6:00 pm **REGISTRATION DESK OPEN** *Santa Fe Convention Center Main Lobby*

7:00 - 7:45
Poster Session V:
Groups C1-C5
Sweeney A-D

Breakfast & Exhibits
Sweeney A-D

7:00 - 7:45
NNS Business Meeting
Coronado

ANNOUNCEMENTS

8:00 - 9:15
PL03
Executive Function After Experimental & Clinical TBI
Sweeney E-F

9:15 - 10:30
S07
Clinical Science of Sports Concussion
Coronado

S08
Operation Brain Trauma Therapy
Sweeney E-F

S09
Influence of Lesion, Stress & Exercise on Blood Brain Barrier Permeability in CNS
O'Keeffe

COFFEE BREAK

11:00 - 12:15
PL04
The Patient's Perspective
Sweeney E-F

12:15 - 1:45
NNS Officers & Councilors Lunch
Santa Fe School of Cooking

FREE TIME LUNCH ON YOUR OWN
All other attendees

1:45- 3:00
S10
Open Communications: TBI
Sweeney E-F

S11
Open Communications: SCI
O'Keeffe

S12
Open Communications: Clinical
Coronado

3:00 - 4:00
Poster Session VI:
Groups C6-C9
Sweeney A-D

"Brain Freeze" Coffee Break & Exhibits

4:00 - 5:00
Poster Session VII:
Groups D1-D6
Sweeney A-D

5:00 - 6:00
Poster Session VIII:
Groups D7-D9
Sweeney A-D

Wine & Cheese & Exhibits

After 6:00
Poster Removal (Groups C & D)

7:00 - 10:00
Social Event:
"An Evening in the Land of Enchantment"
Palace of the Governors & New Mexico History Museum

ticket required

WEDNESDAY, JULY 1 - *All sessions at SFCC*

7:00 am- 4:00 pm **REGISTRATION DESK OPEN** *Santa Fe Convention Center Main Lobby*

7:00 - 7:45
Breakfast
Sweeney A-D

7:00 - 7:45
NNS 2016 Planning Committee Meeting
Teseque

ANNOUNCEMENTS

8:00 - 9:15
PL05
Neuroimaging of Chronic Traumatic Encephalopathy
Sweeney E-F

9:15 - 10:30
S13
Brain Injury: Effects on Physiology & Function
Coronado

S14
Purines-Forgotten Mediators in CNS Injury
Sweeney E-F

S15
Post-Traumatic Epilepsy
O'Keeffe

COFFEE BREAK

11:00 - 11:45
Awards Ceremony
Sweeney E-F

11:45 - 1:00
Student / Post-Doc Lunch
Hosted by NNS Officers & Councilors
Sweeney A-B
ticket required

FREE TIME LUNCH ON YOUR OWN
All other attendees

1:00 - 2:15
PL06
Cell Death is Still Alive
Sweeney E-F

2:15 - 3:45
PL07
Facilitating Transparency in Data Analysis for TBI & SCI Research
Sweeney E-F

3:45 - 4:00
Closing Remarks
Introduction of 2016 President
Sweeney E-F

AGENDA
Sunday, June 28

7:00 am - 6:00 pm	Registration Open	Santa Fe Convention Center
7:30 am - 8:30 am	AANS/CNS Continental Breakfast	O'Keeffe Room @ SFCC
8:00 am - 12:00 pm	Chinese Neurotrauma Association Meeting	New Mexico Room @ La Fonda Hotel
8:30 am - 10:00 am	**AANS01 ACUTE CHALLENGES IN THE UNSTABLE SPINE** [1.5 CME] Chair: Richard Rodgers, MD, Goodman Campbell	O'Keeffe Room @ SFCC
8:30-9:00	AANS01-01 CERVICAL TRACTION FOR THE TREATMENT OF UNSTABLE SUBAXIAL INJURIES Jason Huang, MD, Baylor Scott & White	
9:00-9:30	AANS01-02 LATERAL APPROACH TO SPINE TRAUMA William Smith, MD, PhD, University Medical Center	
9:30-10:00	AANS01-03 TRAUMATIC THORACOLUMBAR SPINAL INJURY: AN ALGORITHM FOR MINIMALLY INVASIVE SURGICAL MANAGEMENT Sanjay Dhall, MD, University of California San Francisco	
10:00 am - 10:30 am	AANS/CNS Coffee Break & Visit Exhibits	Sweeney A-D Ballroom
10:30 am - 12:00 pm	**AANS02 ACUTE SURGICAL CRANIAL TRAUMA - TO DRILL OR NOT TO DRILL: THAT IS THE QUESTION** [1.5 CME] Chair: Jamie Ullman, MD, North Shore University Hospital	O'Keeffe Room @ SFCC
10:30-11:00	AANS02-01 CONTROVERSIES IN INTRACRANIAL MONITORING Martina Stippler, MD, Harvard Medical School	
11:00-11:30	AANS02-02 PRECISION MEDICINE FOR ICP TREATMENT: TCD INDIVIDUALIZES TARGETING COMPLIANCE AND/OR PERFUSION AMELIORATION Gregory Kapinos, MD, Hofstra University	
11:30-12:00	AANS02-03 MANAGEMENT OF ACUTE NEUROVASCULAR INJURY Soren Singel, MD, Baylor Scott & White Health	
12:00 pm - 1:00 pm	FREE TIME / LUNCH ON YOUR OWN	
1:00 pm - 2:30 pm	**AANS03 OUTCOMES AFTER SPINE TRAUMA** [1.5 CME] Chair: Shekar Kurpad, MD, Medical College of Wisconsin	O'Keeffe Room @ SFCC
1:00-1:30	AANS03-01 DOES TIMING MATTER? Aruna Ganju, MD, Northwestern University	
1:30-2:00	AANS03-02 LUMBOSACRAL SPINAL CORD EPIDURAL STIMULATION FOR STANDING AFTER CHRONIC COMPLETE PARALYSIS IN HUMANS Enrico Rejc, PhD, University of Louisville	
2:00-2:30	AANS03-03 ARE STEM CELLS THE ANSWER? Allan Levi, MD, PhD, University of Miami	
1:30 pm - 3:00 pm	Journal of Neurotrauma Editorial Board Meeting	New Mexico Room @ La Fonda Hotel
2:30 pm - 4:00 pm	**AANS04 OUTCOMES AFTER CRANIAL TRAUMA** [1.5 CME] Chair: Uzma Samadani, MD, PhD, New York University	O'Keeffe Room @ SFCC
2:30-3:00	AANS04-01 LONG TERM FUNCTIONAL OUTCOMES AFTER HEMICRANIECTOMY FOR TRAUMA Ann-Christine Duhaime, MD, Massachusetts General Hospital	
3:00-3:30	AANS04-02 HOW STRONG IS THE EVIDENCE LINKING TRAUMA AND/OR TAU TO DEMENTIA? Daniel Perl, MD, Uniformed Services University of the Health Sciences	
3:30-4:00	AANS04-03 PREVALENCE OF VISION PROBLEMS AFTER CONCUSSION IN CHILDREN 11-17 YEARS OLD Christina Master, MD, CHOP/University of Pennsylvania	
3:00 pm - 4:30 pm	WiNTR Business Meeting - *Open to all WiNTR members*	Santa Fe Room @ La Fonda Hotel
4:30 pm - 6:00 pm	NNS Officers & Councilors Meeting	Stiha Room @ La Fonda Hotel
7:00 pm - 8:30 pm	**WELCOME RECEPTION**	La Terazza Rooftop @ La Fonda Hotel

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AGENDA
Monday, June 29

7:00 am - 6:00 pm	Neurotrauma Registration Desk Open	Main Lobby @ SFCC
7:00 am - 8:00 am	Continental Breakfast & Visit Exhibits	Sweeney A-D Ballroom
7:00 am - 8:00 am	**POSTER SESSION I: GROUPS A1-A4** [1.0 CME]	Sweeney A-D Ballroom
7:55 am - 8:00 am	President's Welcome - Helen Bramlett, PhD	Sweeney E-F Ballroom
8:00 am - 9:15 am	**PL01 NEW INVESTIGATORS AND NEW VISIONS FOR CNS INJURY RESEARCH** [1.25 CME] Chairs: Gregory Holmes, PhD, Penn State University; Diane Snow, PhD, University of Kentucky	Sweeney E-F Ballroom
8:00-8:25	PL01-01 ENHANCING RESPIRATORY PLASTICITY FOLLOWING CERVICAL SPINAL CORD INJURY Michael Lane, PhD, Drexel University	
8:25-8:50	PL01-02 RNA SPLICING IN CNS DAMAGE: DIAGNOSING THE INJURED SPLICEOSOME Travis Jackson, PhD, University of Pittsburgh	
8:50-9:15	PL01-03 PLASTICITY IN THE CORTICOSPINAL SYSTEM AFTER SPINAL CORD INJURY Monica Perez, PhD, University of Miami	
9:15 am - 10:30 am	**S01 CLINICALLY RELEVANT MODELS OF NEUROINFLAMMATION AFTER TBI** [1.25 CME] Chairs: Courtney Robertson, MD, Johns Hopkins University; Susanna Rosi, PhD, UC San Francisco	Sweeney E-F Ballroom
9:15-9:40	S01-01 NEUROINFLAMMATION IN THE DEVELOPING BRAIN AFTER INJURY Sujatha Kannan, MD, Johns Hopkins University	
9:40-10:05	S01-02 FRONTAL LOBE INJURY AND HIGHER-ORDER COGNITIVE FUNCTIONS Catharine Winstanley, PhD, University of British Columbia	
10:05-10:30	S01-03 TREATMENTS TO TARGET NEUROINFLAMMATION Cesar Borlongan, PhD, University of South Florida	
9:15 am - 10:30 am	**S02 AGE AND SCI** [1.25 CME] Chair: Kim Anderson-Erisman, PhD, University of Miami	O'Keeffe Room *Sponsored by* CRAIG·H NEILSEN FOUNDATION
9:15-9:40	S02-01 FORTY YEARS OF LIVING WITH SPINAL CORD INJURY - PHYSICAL AND PSYCHOSOCIAL CHANGES OVER TIME Susan Charlifue, PhD, Craig Hospital	
9:40-10:05	S02-02 MUSCLE CHANGES WITH SPINAL CORD INJURY AND AGE Christine Thomas, PhD, University of Miami	
10:05-10:30	S02-03 ACCELERATED AGING AFTER SCI Rachel Cowan, PhD, University of Miami	
9:15 am - 10:30 am	**S03 NOVEL AND EMERGING IMAGING FOR DETECTION AND DIAGNOSIS OF TBI** [1.25 CME] Chairs: Andre Obenaus, PhD, Loma Linda University; Timothy Duong, PhD, UT Health Science Center	Coronado Room
9:15-9:40	S03-01 MAGNETIC RESONANCE IMAGING OF MILD TRAUMATIC BRAIN INJURY Andrew Mayer, PhD, The Mind Research Network	
9:40-10:05	S03-02 MRI OF EXPERIMENTAL TRAUMATIC BRAIN INJURY Timothy Duong, PhD, UT Health Science Center	
10:05-10:30	S03-03 CLINICAL PHENOTYPE OF TRAUMATIC VASCULAR INJURY AND POSSIBLE THERAPEUTIC IMPLICATION Ramon Diaz-Arrastia, MD, PhD, Uniformed Services University of the Health Sciences	
10:30 am - 11:00 am	Coffee Break & Visit Exhibits	Sweeney A-D Ballroom
11:00 am - 12:15 pm	**S04 PROGENITOR CELL THERAPY FOR ADULT TBI: PRECLINICAL FINDINGS AND CLINICAL OUTCOMES** [1.25 CME] Chairs: Linda Ewing-Cobss, PhD, UT Health Science Center; Charles Cox, Jr., PhD, UT Health Science Center	Sweeney E-F Ballroom *Sponsored by* Mission Connect
11:00-11:25	S04-01 CELLULAR THERAPIES FOR TBI: TARGETS AND APPROACH Charles Cox, Jr., MD, UT Health Science Center	
11:25-11:50	S04-02 PRECLINICAL MODELS OF CELLULAR THERAPY: INFLAMMATORY RESPONSE Pramod Dash, PhD, UT Health Science Center	
11:50-12:15	S04-03 NEUROIMAGING AND FUNCTIONAL OUTCOMES AFTER CELLULAR THERAPY FOR SEVERE ADULT TBI Linda Ewing-Cobbs, PhD, UT Health Science Center Jenifer Juranek, PhD, UT Health Science Center	

AGENDA
Monday, June 29

11:00 am - 12:15 pm	**S05 THE ROLE OF apoE AND APOE GENOTYPE IN OUTCOME AFTER TBI** [1.25 CME] Chairs: Mark Burns, PhD, Georgetown University; Barry Jordan, MD, Burke Rehabilitation Hospital	Coronado Room
11:00-11:25	S05-01 APOE4 AS A RISK FACTOR FOR POOR OUTCOME AFTER TBI - CLINICAL AND PRECLINICAL EVIDENCE Mark Burns, PhD, Georgetown University	
11:25-11:50	S05-02 THE EFFECTS OF APOE GENOTYPE ON PROTEOMIC AND LIPIDOMIC RESPONSE TO INJURY IN DIFFERENT MOUSE MODELS OF TBI Fiona Crawford, PhD, The Roskamp Institute	
11:50-12:15	S05-03 NEUROPROTECTIVE AND ANTI-INFLAMMATORY THERAPIES FOR CNS INJURY BASED UPON APOLIPOPROTEIN-E Michael Vitek, PhD, Duke University	
11:00 am - 12:15 pm	**S06 GENETIC DISSECTION OF LOCOMOTOR CIRCUITRY** [1.25 CME] Chair: Scott Whittemore, PhD, University of Louisville	O'Keeffe Room
11:00-11:25	S06-01 CONDITIONAL SILENCING OF PROPRIOSPINAL NEURONS: HOPPING TO A NEW TUNE David Magnuson, PhD, University of Louisville	
11:25-11:50	S06-02 TAKING A STEP TOWARDS MOTOR FUNCTIONAL RECOVERY AFTER SPINAL CORD INJURY: GENETICALLY DEFINING SPINAL MICROCIRCUITS Robert Brownstone, MD, PhD, Dalhousie University	
11:50-12:15	S06-03 MUSCLE SPINDLE FEEDBACK DIRECTS LOCOMOTOR RECOVERY AND CIRCUIT REORGANIZATION AFTER SCI Aya Takeoka, PhD, University of Basel	
12:15 pm - 12:30 pm	Lunch Pickup for WiNTR Session attendees	Lamy Foyer
12:30 pm - 1:45 pm	**WLW WiNTR LUNCH SESSION: HUMAN TBI NEUROPATHOLOGY** [1.25 CME] Chairs: William Stewart, MBChB, PhD, Southern General Hospital; Patricia Washington, PhD, Georgetown University	Peralta / Lamy Room
12:30-12:55	WLW1-01 EXPERIENCE IN EXAMINATION OF HUMAN TBI TISSUE: A NEGLECTED ART William Stewart, MBChB, PhD, Southern General Hospital	
12:55-1:20	WLW1-02 BI-DIRECTIONAL TRANSLATIONAL STUDIES IN TBI: EXPERIMENTAL DESIGN USING HUMAN SAMPLES Victoria Johnson, PhD, University of Pennsylvania	
1:20-1:45	WLW1-03 THE GLASGOW TRAUMATIC BRAIN INJURY ARCHIVE Jennifer Hay, University of Glasgow	
12:15 pm - 1:45 pm	FREE TIME - LUNCH ON YOUR OWN	
1:45 pm - 3:00 pm	**PL02 THERAPEUTIC HYPOTHERMIA AND TARGETED TEMPERATURE MANAGEMENT AFTER SCI AND TBI - IS THE VERDICT STILL OUT?** [1.25 CME] Chair: W. Dalton Dietrich, PhD, University of Miami	Sweeney E-F Ballroom *Sponsored by* ZOLL
1:45-2:10	PL02-01 PERSPECTIVES ON HYPOTHERMIA AFTER TBI AND SCI - REVIEW OF NEW BASIC RESEARCH IN TEMPERATURE MANAGEMENT W. Dalton Dietrich, PhD, University of Miami	
2:10-2:35	PL02-02 HYPOTHERMIA FOR TRAUMATIC BRAIN INJURY: IT WORKS WITH CORRECT PATIENT SELECTION David Okonkwo, MD, PhD, University of Pittsburgh	
2:35-3:00	PL02-03 THERAPEUTIC HYPOTHERMIA AND TARGETED TEMPERATURE MANAGEMENT AFTER SCI AND TBI - IS THE VERDICT STILL OUT? Allan Levi, MD, PhD, University of Miami	
3:00 pm - 3:30 pm	"Sweet Treat" Coffee Break & Visit Exhibits	Sweeney A-D Ballroom
3:00 pm - 4:00 pm	**POSTER SESSION II: GROUPS A5-A8 and T1-T20** [1.0 CME] Student Competition Final Judging	Sweeney A-D Ballroom
4:00 pm - 5:00 pm	**POSTER SESSION III: GROUPS B1-B4** [1.00 CME]	
5:00 pm - 6:00 pm	**POSTER SESSION III: GROUPS B5-B7** [1.00 CME]	
5:00 pm - 6:00 pm	Wine & Cheese Reception with Exhibitors	Sweeney A-D Ballroom
6:00 pm - 8:00 pm	**WNR WiNTR Mentoring & Networking Reception** [1.00 CME] WNR-1 CAREER DEVELOPMENT IN NEUROTRAUMA RESEARCH Mary Ellen Michel, PhD, NIH / NICHD	Georgia O'Keeffe Museum *Sponsored by* WiNTR Women in Neurotrauma Research

AGENDA
Tuesday, June 30

7:00 am - 6:00 pm	Neurotrauma Registration Desk Open	Main Lobby @ SFCC
7:00 am - 8:00 am	Continental Breakfast & Visit Exhibits	Sweeney A-D Ballroom
7:00 am - 7:45 am	NNS Society Business Meeting	Peralta/Lamy Room
7:00 am - 8:00 am	**POSTER SESSION V: GROUPS C1-C5** [1.0 CME]	Sweeney A-D Ballroom
7:55 am - 8:00 am	President's Announcements - Helen Bramlett, PhD	Sweeney E-F Ballroom
8:00 am - 9:15 am	**PL03 EXECUTIVE FUNCTION AFTER EXPERIMENTAL AND CLINICAL TBI** [1.25 CME] Chairs: Anthony Kline, PhD, University of Pittsburgh; Corina Bondi, PhD, University of Pittsburgh	Sweeney E-F Ballroom
8:00-8:25	PL03-01 A COMBINED THERAPY OF ENVIRONMENTAL ENRICHMENT AND CITALOPRAM AMELIORATES ATTENTIONAL SET-SHIFTING PERFORMANCE AFTER BRAIN TRAUMA Corina Bondi, PhD, University of Pittsburgh	
8:25-8:50	PL03-02 MODELING CHRONIC COGNITIVE DYSFUNCTION AFTER TBI: WHERE DO WE GO FROM HERE? Cole Vonder Haar, PhD, University of British Columbia	
8:50-9:15	PL03-03 EXECUTIVE FUNCTION AFTER TRAUMATIC BRAIN INJURY: CHALLENGES IN ITS ASSESSMENT & MANAGEMENT William Barr, PhD, New York University	
9:15 am - 10:30 am	**S07 CLINICAL SCIENCE OF SPORTS CONCUSSION** [1.25 CME] Chairs: Christopher Giza, MD, UCLA; Michelle LaPlaca, PhD, Georgia Institute of Technology/Emory University	Coronado Room
9:15-9:40	S07-01 EPIDEMIOLOGY OF SPORTS CONCUSSIONS R. Dawn Comstock, PhD, University of Colorado	
9:40-10:05	S07-02 THE CHALLENGES OF CONCUSSION DIAGNOSIS IN ATHLETES Kevin Guskiewicz, PhD, University of North Carolina	
10:05-10:30	S07-03 EVIDENCE BASED ASSESSMENT TO SPORT CONCUSSION MANAGEMENT Gerard Gioia, PhD, Children's National Medical Center	
9:15 am - 10:30 am	**S08 OPERATION BRAIN TRAUMA THERAPY: THE THRILL OF VICTORY AND THE AGONY OF DEFEAT** [1.25 CME] Chair: Frank Tortella, PhD, Walter Reed Army Institute of Research	Sweeney E-F Ballroom
9:15-9:40	S08-01 MULTI-CENTER PRE-CLINICAL THERAPY SCREENING IN TBI: RESULTS OF THE OBTT CONSORTIUM Patrick Kochanek, MD, University of Pittsburgh	
9:40-10:05	S08-02 A UNIQUE TOOL FOR CROSS MODEL COMPARISON IN PRECLINICAL TRAUMATIC BRAIN INJURY Deborah Shear, PhD, Walter Reed Army Institute of Research	
10:05-10:30	S08-03 BIOMARKERS AS A WINDOW ON TBI MODELING AND THERAPEUTIC EFFICACY: RESULTS OF THE OBTT CONSORTIUM Stefania Mondello, MD, PhD, University of Messina	
9:15 am - 10:30 am	**S09 INFLUENCE OF LESION, STRESS AND EXERCISE ON BLOOD BRAIN BARRIER PERMEABILITY IN THE CNS** [1.25 CME] Chair: D. Michele Basso, PhD, Ohio State University	O'Keeffe Room
9:15-9:40	S09-01 REMOTE BLOOD BRAIN BARRIER DISRUPTION AFTER MID-THORACIC SPINAL CORD INJURY D. Michele Basso, EdD, Ohio State University	
9:40-10:05	S09-02 MICROGLIAL ACTIVATION AND THE RECRUITMENT OF MONOCYTES TO THE CNS: LESSONS LEARNED FROM MODELS OF PSYCHOLOGICAL STRESS AND SCI Jonathan Godbout, PhD, Ohio State University	
10:05-10:30	S09-03 EXERCISE AFTER TRAUMATIC BRAIN INJURY: IS IT A DOUBLE-EDGED SWORD? Grace Griesbach, PhD, Centre for NeuroSkills	
10:30 am - 11:00 am	Coffee Break & Visit Exhibits	Sweeney A-D Ballroom
11:00 am - 12:15 pm	**PL04 THE PATIENT'S PERSPECTIVE : RECOVERY FROM SEVERE TBI** [1.25 CME] Chair: Kim Anderson-Erisman, PhD, University of Miami	Sweeney E-F Ballroom
11:00-11:40	PL04-01 DOES THIS WHEELCHAIR MAKE MY BUTT LOOK BIG? Briana Walker-Tavano, Speaker, Briana Walker, Intl.	
11:40-12:15	PL04-02 RECOVERY FROM SEVERE TBI: PATIENT PERSPECTIVE Cathy Liu, MD, University of California, Davis Kiarash Shahlaie, MD, PhD, University of California, Davis	

AGENDA
Tuesday, June 30

12:15 pm - 1:45 pm	NNS Officers & Councilors Lunch	Santa Fe School of Cooking
12:15 pm - 1:45 pm	FREE TIME - LUNCH ON YOUR OWN	
1:45 pm - 3:00 pm	**S10 OPEN COMMUNICATIONS: TBI** [1.25 CME] Chair: Ramona Hicks, PhD, One Mind	Sweeney E-F Ballroom
1:45-2:00	S10-01 PREVENTING POSTTRAUMATIC EPILEPTOGENESIS BY STIMULATING CORTICAL EXCITATORY ACTIVITY AFTER TBI Xiaoming Jin, PhD, Indiana University	
2:00-2:15	S10-02 CHRONIC NEUROPHYSIOLOGICAL RECORDING OF THE HIPPOCAMPUS IN AWAKE BEHAVING SWINE AFTER DIFFUSE BRAIN INJURY John Wolf, PhD, University of Pennsylvania	
2:15-2:30	S10-03 ABBREVIATED ENVIRONMENTAL ENRICHMENT CONFERS ROBUST NEUROBEHAVIORAL AND COGNITIVE BENEFITS IN BRAIN INJURED FEMALE RATS Hannah Radabaugh, University of Pittsburgh	
2:30-2:45	S10-04 NEUROINFLAMMATORY MYELOID CELL PROCESSES ASSOCIATE WITH DIFFUSELY INJURED AXONS FOLLOWING MILD TRAUMATIC BRAIN INJURY IN MICROPIGS Audrey Lafrenaye, PhD, Virginia Commonwealth University	
2:45-3:00	S10-05 CHARACTERIZATION OF ENDOGENOUS BRAIN-DERIVED NEUROTROPHIC FACTOR EXPRESSION IN RESPONSE TO PENETRATING BALLISTIC-LIKE INJURY Ying Deng-Bryant, PhD, Walter Reed Army Institute of Research	
1:45 pm - 3:00 pm	**S11 OPEN COMMUNICATIONS: SCI** [1.25 CME] Chair: Philip Popovich, PhD, Ohio State University	O'Keeffe Room
1:45-2:00	S11-01 THE CGRP8-37 RECOMBINANT PEPTIDE CONSTRUCT TO REDUCE CHRONIC PAIN FROM RAT SPINAL CORD INJURY Chenxu Han, PhD, Florida International University	
2:00-2:15	S11-02 LONGITUDINAL OPTOGENETIC MAPPING OF THE CORTICOSPINAL TRACT AS A NOVEL APPROACH FOR FUNCTIONAL EVALUATION OF SPINAL CORD INJURY Xiaoming Jin, PhD, Indiana University	
2:15-2:30	S11-03 3D IMAGING OF AXONS IN TRANSPARENT SPINAL CORDS FROM RODENTS AND NON-HUMAN PRIMATES Pantelis Tsoulfas, MD, University of Miami	
2:30-2:45	S11-04 TARGETING THE TRPV4 CHANNEL TO REDUCE INFLAMMATION AND IMPROVE OUTCOME FOLLOWING SCI Raymond Grill, PhD, University of Mississippi	
2:45-3:00	S11-05 ATTENUATING GASTROINTESTINAL VASCULAR PERMEABILITY AFTER SPINAL CORD INJURY Juan Herrera, PhD, UT Health Medical School	
1:45 pm - 3:00 pm	**S12 OPEN COMMUNICATIONS: CLINICAL** [1.25 CME] Chair: Bruce Lyeth, PhD, University of California, Davis	Coronado Room
1:45-2:00	S12-01 A PROGNOSTIC MODEL FOR DETERMINING ONE-MONTH OUTCOMES IN MILD TRAUMATIC BRAIN INJURY Hayley Falk, Johns Hopkins University	
2:00-2:15	S12-02 AN INITIAL EVALUATION OF THE NINDS PHENOTYPING COMMON DATA ELEMENTS FOR TRAUMATIC BRAIN INJURY Leighton Chan, PhD, National Institutes of Health	
2:15-2:30	S12-03 ADOLESCENT TRAUMATIC BRAIN INJURY INCREASES ALCOHOL CONSUMPTION AND REWARD IN FEMALE MICE Zachary Weil, PhD, Ohio State University	
2:30-2:45	S12-04 SINGLE EPISODE OF SEVERE AXONAL INJURY IN HUMANS IS ASSOCIATED WITH PATHOLOGY RESEMBLING CHRONIC TRAUMATIC ENCEPHALOPATHY Daniel Perl, MD, Uniformed Services University of the Health Sciences	
2:45-3:00	S12-05 TRAUMATIC AXONAL INJURY IN THE LIVING HUMAN BRAIN: CONCORDANCE OF MICRODIALYSIS AND ADVANCED MRI APPROACHES David Brody, MD, PhD, Washington University St. Louis	
3:00 pm - 3:30 pm	"Brain Freeze" Break & Visit Exhibits	Sweeney A-D Ballroom
3:00 pm - 4:00 pm	**POSTER SESSION VI: GROUPS C6-C9** [1.0 CME]	Sweeney A-D Ballroom
4:00 pm - 5:00 pm	**POSTER SESSION VII: GROUPS D1-D6** [1.00 CME]	
5:00 pm - 6:00 pm	**POSTER SESSION VIII: GROUPS D7-D9** [1.00 CME]	
5:00 pm - 6:00 pm	Wine & Cheese Reception with Exhibitors	Sweeney A-D Ballroom
7:00 pm - 10:00 pm	**NMHM An Evening in the Land of Enchantment** *Sponsored by the National Neurotrauma Society - Ticket Required*	NM History Museum / Palace of the Governors

AGENDA
Wednesday, July 1

7:00 am - 4:00 pm	Neurotrauma Registration Desk Open	Main Lobby @ SFCC
7:00 am - 8:00 am	Continental Breakfast	Sweeney A-D Ballroom
7:00 am - 8:00 am	NNS 2016 Planning Committee Meeting	Teseque Room (2nd floor)
7:55 am - 8:00 am	President's Announcements - Helen Bramlett, PhD	Sweeney E-F Ballroom
8:00 am - 9:15 am	**PL05 NEUROIMAGING OF CHRONIC TRAUMATIC ENCEPHALOPATHY** [1.25 CME] Chair: Samuel Gandy, MD, PhD, Icahn School of Medicine at Mount Sinai	Sweeney E-F Ballroom
8:00-8:25	PL05-01 NEUROIMAGING CORRELATES OF REPETITIVE LOW-LEVEL BLAST EXPOSURE IN MILITARY SERVICE MEMBERS James Stone, MD, PhD, University of Virginia	
8:25-8:50	PL05-02 NEUROIMAGING OF BOXERS Barry Jordan, MD, Burke Rehabilitation Hospital	
8:50-9:15	PL05-03 THE NEUROANATOMY OF CTE Dara Dickstein, PhD, Icahn School of Medicine at Mount Sinai	
9:15 am - 10:30 am	**S13 BRAIN INJURY: EFFECTS ON PHYSIOLOGY AND FUNCTION BEYOND THE BRAIN** [1.25 CME] Chairs: Jonathan Lifshitz, PhD, University of Arizona, Emily Swartz-Besecker, PhD, Gettysburg College	Coronado Room
9:15-9:40	S13-01 HEPATIC AND SPLENIC CONTRIBUTIONS TO TRAUMATIC BRAIN INJURY Lee Shapiro, MD, Texas A&M Health Science Center	
9:40-10:05	S13-02 NEUROGENIC IMMUNE DEFICIENCY AFTER SPINAL CORD INJURY: MECHANISMS OF ACTION AND THERAPEUTIC OPPORTUNITIES Phillip Popovich, PhD, Ohio State University	
10:05-10:30	S13-03 INTESTINAL BARRIER DYSFUNCTION AFTER TRAUMATIC BRAIN INJURY Vishal Bansal, MD, University of California, San Diego	
9:15 am - 10:30 am	**S14 PURINES - FORGOTTEN MEDIATORS IN CNS INJURY** [1.25 CME] Chair: Patrick Kochanek, MD, University of Pittsburgh	Sweeney E-F Ballroom *Sponsored by* ISN International Society for Neurochemistry
9:15-9:40	S14-01 ROLE OF THE 2',3'-cAMP-ADENOSINE PATHWAY IN TRAUMATIC BRAIN INJURY Edwin Jackson, PhD, University of Pittsburgh	
9:40-10:05	S14-02 ROLE OF ADENOSINE IN POSTTRAUMATIC SEIZURES AND EPILEPSY: A POTENTIAL NEW TARGET Detlev Boison, PhD, Legacy Research Institute, Dow Neurobio Laboratories	
10:05-10:30	S14-03 URATE - A NOVEL POTENTIAL THERAPY IN CNS INJURY AND NEURODEGENERATION Michael Schwarzschild, MD, PhD, Massachusetts General Hospital	
9:15 am - 10:30 am	**S15 POST-TRAUMATIC EPILEPSY: MECHANISMS AND MANIFESTATIONS** [1.25 CME] Chair: Bridgette Semple, PhD, University of Melbourne	O'Keeffe Room *Sponsored by* Eisai
9:15-9:40	S15-01 CLINICAL RESEARCH INSIGHTS INTO PERSONAL BIOLOGY AND BIOSUSCEPTIBILTIY WITH EPILEPTOGENESIS AND POST-TRAUMATIC EPILEPSY Amy Wagner, MD, University of Pittsburgh	
9:40-10:05	S15-02 SEIZURE SUSCEPTIBILITY AFTER TRAUMATIC INJURY TO THE PEDIATRIC BRAIN Bridgette Semple, PhD, University of Melbourne	
10:05-10:30	S15-03 NON-CONVULSIVE SEIZURES OBSERVED 1 YEAR FOLLOWING TRAUMATIC BRAIN INJURY Thomas Sick, PhD, University of Miami	
10:30 am - 11:00 am	Coffee Break	Sweeney A-D Ballroom
11:00 am - 11:45 am	**AWARDS CEREMONY & iWatch Drawing**	Sweeney E-F Ballroom
11:45 am - 1:00 pm	**Student / Post-Doc Lunch with NNS Officers & Councilors**	Sweeney A-B Ballroom
11:45 am - 1:00 pm	FREE TIME - LUNCH ON YOUR OWN	
1:00 pm - 2:15 pm	**PL06 CELL DEATH IS STILL ALIVE** [1.25 CME] Chairs: Michal Hetman, MD, PhD, University of Louisville; Scott Whittemore, PhD, University of Louisville	Sweeney E-F Ballroom
1:00-1:25	PL06-01 AUTOPHAGY AND NEURODEGENERATION Esperanza Arias, PharmD, PhD, Albert Einstein College of Medicine	

AGENDA
Wednesday, July 1

1:25-1:50	PL6-02 HEAVY METAL KILLS: ZINC IS AN ENDOGENOUS SUPPRESSOR OF CELL SURVIVAL AND AXON REGENERATION AFTER OPTIC NERVE INJURY Larry Benowitz, PhD, Boston Children's Hospital/Harvard Medical School	
1:50-2:15	PL06-03 TARGETING THE HOMEOSTATIC ARM OF THE ER STRESS PATHWAY IMPROVES FUNCTIONAL RECOVERY AFTER SCI Sujata Saraswat, PhD, University of Louisville	
2:15 pm - 3:45 pm	**PL07 FACILITATING TRANSPARENCY IN DATA ANALYSIS FOR TBI AND SCI RESEARCH** [1.5 CME] Chair: Denes Agoston, MD, PhD, Uniformed Services University	Sweeney E-F Ballroom
2:15-2:37	PL07-01 INTRODUCTION ABOUT BIG AND SMALL DATA IN TBI AND SCI Denes Agoston, MD, PhD, Uniformed Services University	
2:37-3:00	PL07-02 TOWARDS A ROADMAP FOR TRANSLATION OF CANDIDATE TREATMENTS FOR SPINAL CORD INJURY Wolfram Tetzlaff, MD, PhD, University of British Columbia, ICORD	
3:00-3:22	PL07-03 PRECLINICAL TRAUMATIC BRAIN INJURY COMMON DATA ELEMENTS: TOWARDS A COMMON LANGUAGE ACROSS LABORATORIES Douglas H. Smith, MD, University of Pennsylvania	
3:22-3:45	PL07-04 FACILITATING REPRODUCIBILITY AND DATA INTEGRATION FOR SCI RESEARCH WITH MIASCI AND REGENBASE Vance Lemmon, PhD, University of Miami	
3:45 pm - 4:00 pm	**CLOSING REMARKS & INTRODUCTION OF 2016 PRESIDENT** Helen Bramlett, PhD Diane Snow, PhD	Sweeney E-F Ballroom

STUDENT POSTER COMPETITION FINALISTS & POSTER SET UP TIMES

T1-01 3:00 PM
Morioka, Kazuhito; Brain and Spinal Injury Center (BASIC), University of California, San Francisco
EARLY HINDLIMB UNLOADING PRODUCES CHRONIC BIOMECHANICAL, PHYSIOLOGICAL AND MOLECULAR SIGNATURES OF MALADAPTIVE PLASTICITY IN SCI

T1-02 3:15 PM
Deng, Lingxiao; Indiana University
DENDRITIC MORPHOLOGY AND NEUROTRANSMITTER TYPE OF THORACIC DESCENDING PROPRIOSPINAL NEURONS IN SHAM, AXOTOMY, AND GDNF TREATMENT

T1-03 3:30 PM
Ganpule, Shailesh; Johns Hopkins
COMPUTATIONAL MODELING AND VALIDATION OF BRAIN DEFORMATION IN HUMAN VOLUNTEERS WITH RELEVANCE TO TRAUMATIC BRAIN INJURY

T1-04 3:45 PM
Merkel, Steven; Temple University School of Medicine
ADOLESCENT BRAIN INJURY INDUCES CHRONIC MESOLIMBIC NEUROINFLAMMATION THAT COINCIDES WITH ENHANCED ADDICTION-LIKE BEHAVIOR IN MICE

T1-05 4:00 PM
Muccigrosso, Megan; The Ohio State University
COGNITIVE DEFICITS DEVELOP 30D AFTER TBI AND ARE EXAGGERATED BY MICROGLIA-ASSOCIATED REACTIVITY TO PERIPHERAL IMMUNE CHALLENGE

T1-06 3:00 PM
Daiutolo, Brittany; Thomas Jefferson University
GENETIC AND PHARMACOLOGICAL MODULATION OF TRIGEMINAL PAIN MOLECULES IN A MODEL OF TRAUMATIC BRAIN INJURY

T1-07 3:15 PM
Hong, James; Toronto Western Research Institute
LEVEL-SPECIFIC OPTIMIZATION OF CELLULAR INTERVENTION IN SPINAL CORD INJURY - A NEW PARADIGM

T1-08 3:30 PM
Greco, Tiffany; UCLA
KETOGENIC DIET DECREASES OXIDATIVE STRESS AND IMPROVES MITOCHONDRIAL RESPIRATORY COMPLEX ACTIVITY

T1-09 3:45 PM
Ogle, Sarah; University of Arizona
EXPERIMENTAL DIFFUSE TRAUMATIC BRAIN INJURY INCREASES ASTROCYTE-SECRETED THROMBOSPONDIN-1 IN THE THALAMUS

T1-10 4:00 PM
Nielson, Jessica; University of California San Francisco
PERIOPERATIVE HYPERTENSION PREDICTS WORSE FUNCTIONAL RECOVERY FOLLOWING THORACIC SPINAL CORD INJURY IN RATS

T1-11 3:00 PM
McGuire, Jennifer; University of Cincinnati
KINASES REGULATING GLUTAMATE TRANSPORTERS ARE DIFFERENTIALLY ACTIVATED AFTER LATERAL FLUID PERCUSSION

T1-12 3:15 PM
Muradashvili, Nino; University of Louisville
ADIPOSE STROMAL VASCULAR FRACTION CELL TREATMENT MITIGATES INCREASED CEREBROVASCULAR PERMEABILITY AFTER TRAUMATIC BRAIN INJURY

T1-13 3:30 PM
Harris, James; University of Pennsylvania
NEURONAL PLASMALEMMAL PERMEABILITY/DENDRITIC BEADING IN THE HIPPOCAMPUS FOLLOWING DIFFUSE BRAIN INJURY IN SWINE

T1-14 3:45 PM
Myrga, John; University of Pittsburgh
COMT AND ANKK1 GENETICS INTERACT WITH DEPRESSION TO INFLUENCE BEHAVIOR FOLLOWING MODERATE/SEVERE TBI

T1-15 4:00 PM
Lajud Avila, Naima; University of Pittsburgh
DELAYED AND ABBREVIATED ENVIRONMENTAL ENRICHMENT AFTER EXPERIMENTAL TRAUMATIC BRAIN INJURY INCREASES HIPPOCAMPAL NEUROGENESIS

T1-16 3:00 PM
Han, Kihwan; University of Texas at Dallas
DEPRESSIVE SYMPTOMS ALTER AMYGDALA CONNECTIVITY IN TRAUMATIC BRAIN INJURY

T1-17 3:15 PM
Dennis, Emily; USC Keck School of Medicine
SLOWED CALLOSAL FUNCTION IN TBI LINKED TO IMPAIRED WHITE MATTER INTEGRITY

T1-18 3:30 PM
Brabazon, Fiona; USUHS
INTRANASAL INSULIN TREATMENT OF TRAUMATIC BRAIN INJURY: EFFECTS ON MEMORY AND CEREBRAL METABOLISM

T1-19 3:45 PM
Todani, Masaki; Virginia Commonwealth University
THE ROLE OF THE ATP-SENSITIVE POTASSIUM CHANNEL IN THE VASCULAR DYSFUNCTION ASSOCIATED WITH REPETITIVE MILD TRAUMATIC BRAIN INJURY

T1-20 4:00 PM
Holleran, Laurena; Washington University St. Louis
ADVANCED DIFFUSION MRI-BASED RADIOLOGICAL-PATHOLOGICAL CORRELATIONS IN CHRONIC TRAUMATIC ENCEPHALOPATHY

Top Poster Finalists

Author Set-Up Time:
Sunday beginning at 1:00 pm
Poster Viewing Times:
Posters should remain on display from set up until 6:00 pm on Tuesday
Final Competition Judging
Monday from 3:00 to 4:00 pm
Author Removal Time:
Tuesday from 6:00 – 6:30 pm

NNS assumes no responsibility for posters left on boards after the poster removal period.

Poster Sessions A & B

Author Set-Up Time:
Sunday beginning at 1:00 pm
Poster Viewing Times:
Posters should remain on display from set up until 6:00 pm on Monday
Group A Presentations
Monday from 7:00 to 8:00 am
Monday from 3:00 to 4:00 pm
Group B Presentations
Monday from 4:00 to 5:00 pm
Monday from 5:00 to 6:00 pm
Author Removal Time:
Monday from 6:00 – 6:30 pm

Poster Sessions C & D

Author Set-Up Time:
Monday beginning at 6:00 pm
Poster Viewing Times:
Posters should remain on display from set up until 6:00 pm on Tuesday
Group C Presentations
Tuesday from 7:00 to 8:00 am
Tuesday from 3:00 to 4:00 pm
Group D Presentations
Tuesday from 4:00 to 5:00 pm
Tuesday from 5:00 to 6:00 pm
Author Removal Time:
Tuesday from 6:00 – 6:30 pm

POSTER SESSION I

CELL DEATH

A1-01 7:00 AM
Effgen, Gwen; Columbia University
REPETITIVE PRIMARY BLAST-INDUCED VULNERABILITY AND DEFICITS IN LONG-TERM POTENTIATION WITHOUT CELL DEATH

A1-02 7:15 AM
Hetman, Michal; Kentucky Spinal Cord Injury Research Ctr
INHIBITION OF RNA-POLYMERASE-1 PROTECTS OLIGODENDROCYTES AGAINST ENDOPLASMIC RETICULUM STRESS

A1-03 7:30 AM
Miller, Anna; Medical College of Wisconsin
USE OF AN IN VITRO MODEL TO STUDY THE ACUTE EFFECTS OF BLAST OVERPRESSURE ON NEURONS AND GLIAL CELLS

A1-04 7:00 AM
Chao, Honglu; Nanjing Medical University
INHIBITION OF CA2+-INDEPENDENT PLA2Ÿ EXACERBATED THE MECHANICAL STRETCH INJURY IN PRIMARY CORTICAL NEURONS

A1-05 7:15 AM
Shellington, David; UCSD
A NOVEL METHOD FOR TRAUMATIC INJURY OF ORGANOTYPIC HIPPOCAMPAL SLICE CULTURES

A1-06 7:30 AM
Lipinski, Marta; University of Maryland, Baltimore
DISRUPTED AUTOPHAGY AFTER SPINAL CORD INJURY IS ASSOCIATED WITH ER STRESS AND NEURONAL CELL DEATH

A1-07 7:00 AM
Lipinski, Marta; University of Maryland, Baltimore
LYSOSOMAL DAMAGE LEADS TO INHIBITION OF AUTOPHAGY & CONTRIBUTES TO NEURONAL CELL DEATH AFTER TBI

A1-08 7:15 AM
Parsley, Maggie; University of Texas Medical Branch
SILICONE PAD DEMONSTRATES SIMILAR LEVEL OF EFFECTIVENESS AS NEOPRENE PAD ON FLUID PERCUSSION INJURY DEVICE

A1-09 7:30 AM
Zeng, Yaping; University of Texas Medical Branch
PROTECTIVE EFFECTS OF ESTROGEN IN VASCULAR SMOOTH MUSCLE CELLS AFTER RAPID-STRETCH INJURY

SECONDARY INJURY

A2-01 7:00 AM
Yonan, Charles; Avanir Pharmaceuticals, Inc.
SAFETY, TOLERABILITY, AND EFFECTIVENESS OF DEXTROMETHORPHAN/QUINIDINE FOR PSEUDOBULBAR AFFECT IN TRAUMATIC BRAIN INJURY: PRISM-II

A2-02 7:00 AM
Vedantam, Aditya; Baylor College of Medicine
DOES A HIGHER HEMOGLOBIN TRANSFUSION THRESHOLD AFFECT THE RISK OF PROGRESSIVE HEMORRHAGE AFTER SEVERE TRAUMATIC BRAIN INJURY?

A2-03 7:15 AM
Zhao, Shu; Indiana University School of Medicine
THE ROLE OF 7,8-DIHYDROXYFLAVONE IN PREVENTING DENDRITE DEGENERATION IN CORTEX AFTER MODERATE TRAUMATIC BRAIN INJURY

A2-04 7:30 AM
Liu, Nai-Kui; Indiana University School of Medicine
PROFILE OF PHOSPHOLIPID ALTERATIONS OF SPINAL CORD INJURY: LIPIDOMIC ANALYSIS

A2-05 7:00 AM
Sashindranath, Maithili; Monash University
DOES THE PLASMINOGEN ACTIVATION SYSTEM REGULATE POST-TRAUMATIC DEMENTIA?

A2-06 7:15 AM
Mullah, Saad; Naval Medical Research Center
THE PERFLUOROCARBON NVX-108 INCREASED BRAIN TISSUE OXYGENATION AFTER CONTROLLED CORTICAL IMPACT BRAIN INJURY IN THE RAT

A2-07 7:30 AM
Abutarboush, Rania; Naval Medical Research Center/ HJF
OXYGEN CARRIER M-101 DID NOT CAUSE VASOCONSTRICTION AND IMPROVED CEREBRAL OXYGENATION AFTER TBI IN RATS

A2-08 7:00 AM
Yan, Wei; The Second Affiliated Hospital, Zhejiang University
TREATMENT AND RISK FACTORS FOR POST-TRAUMATIC EXTERNAL HYDROCEPHALUS FOLLOWING DECOMPRESSIVE CRANIECTOMY

A2-09 7:15 AM
Jodoin, Marianne; Universite de Montreal
THE INCIDENCE RATE OF MILD TRAUMATIC BRAIN INJURY IN PATIENTS SUFFERING FROM AN UPPER OR LOWER LIMB FRACTURE

A2-10 7:30 AM
Gurkoff, Gene; University of California, Davis
CALCIUM AND GLUTAMATE SIGNALING AFTER TBI VISUALIZED IN-VITRO USING GENE-ENCODED MOLECULAR SENSORS GCAMP6 AND IGLUSNFR.

A2-11 7:00 AM
Yontuas, Heather; University Of Kentucky
A "NEET" MITOCHONDRIAL TARGET FOR TBI: THE IMPORTANCE OF MITONEET IN PIOGLITAZONE MEDIATED NEUROPROTECTION

A2-12 7:00 AM
Nazar, Ryan; University of Louisville
DANTE: DEFORMITY, ANKYLOSIS, NEUROLOGIC DEFICIT, TRANSLATION, EXTENSIVE TRAUMA. A MNEMONIC PREDICTING SPINAL INSTABILITY

A2-13 7:15 AM
Harrison, Emily; University of Nebraska Medical Center
INCREASES IN INFLAMMATION-ASSOCIATED MIRNAS AND CHARACTERIZATION OF LONG-TERM OUTCOMES IN A CCI MODEL OF TBI

A2-14 7:30 AM
Wu, Ping; University of Texas Medical Branch
ENHANCING HIPPOCAMPAL NEURON SURVIVAL AFTER MULTIPLE BRAIN INJURIES BY HUMAN NEURAL STEM CELL-SECRETED GLIAL CELL LINE-DERIVED NEU

A2-15 7:00 AM
Guptarak, Jutatip; University of Texas Medical Branch
ACUTE EFFECTS OF 17ÃŸ-ESTRADIOL ON OXIDATIVE STRESS RESPONSE PROTEINS AFTER TBI

A2-16 7:15 AM
Alshareef, Ahmed; University of Virginia
CHARACTERIZATION OF BRAIN MATERIAL PROPERTIES FOLLOWING BRAIN BLAST INJURY

A2-17 7:30 AM
Fortune, Ryan; UTHealth GSBS
SPINAL CORD INJURY CAUSES DISTINCT ACUTE AND CHRONIC PHASES IN THE TESTES AND BLOOD TESTES BARRIER OF A SPRAGUE-DAWLEY RAT MODEL

A2-18 7:00 AM
Friess, Stuart; Washington University at St. Louis
DELAYED HYPOXIA FOLLOWING TRAUMATIC BRAIN INJURY EXACERBATES AXONAL INJURY

BLOOD-BRAIN BARRIER

A3-01 7:15 AM
Bharadwaj, Vimala; Arizona State University
EVALUATING THE POTENTIAL FOR NANOPARTICLE DELIVERY AFTER TRAUMATIC BRAIN INJURY

A3-02 7:30 AM
Rossi, Janet; LSUHSC/Children's Hospital
ISG15 INTERACTS WITH JUNCTIONAL PROTEINS PRIOR TO BBB DISRUPTION FOLLOWING TBI IN YOUNG MICE

A3-03 7:00 AM
Lutton, Evan; Temple University School of Medicine
ENDOTHELIAL TARGETED ANTIOXIDANT ENZYME THERAPY TO COMBAT SECONDARY INJURY AND PRESERVE BBB INTEGRITY FOLLOWING EXPERIMENTAL TBI

A3-04 7:00 AM
Browning, Jenny; Walter Reed Army Institute of Research
PROFILE OF BLOOD BRAIN BARRIER DISRUPTION FOLLOWING SINGLE AND REPEATED CLOSED HEAD IMPACT CONCUSSION IN RATS

PEDIATRIC

A4-01 7:15 AM
Clark, Robert; Children's Hospital of Pittsburgh
PHASE I TRIAL OF N-ACETYLCYSTEINE IN COMBINATION WITH PROBENECID IN CHILDREN AFTER SEVERE TBI

A4-02 7:30 AM
Jernberg, Jennifer; Johns Hopkins
FATTY ACID OXIDATION IS INCREASED SELECTIVELY IN ASTROCYTES OF INJURED HIPPOCAMPUS AFTER TBI

A4-03 7:00 AM
Robertson, Courtney; Johns Hopkins School of Medicine
20-HETE INHIBITION IMPROVES OUTCOME IN A PEDIATRIC RAT MODEL OF TRAUMATIC BRAIN INJURY

A4-04 7:15 AM
Costine, Beth; Massachusetts Gen. Hospital/ Harvard Med.
LARGE-ANIMAL COMBINED INSULT MODEL FOR INFLICTED BRAIN INJURY IN INFANCY

A4-05 7:30 AM
Bayir, Hulya; Safar Center for Resuscitation Research
MAGNETIC RESONANCE SPECTROSCOPY IMAGING OF THE HIPPOCAMPUS AT 7T AFTER MILD TBI IN IMMATURE BRAIN

A4-06 7:00 AM
Fischer, Jesse; University of Houston
CHRONIC WHITE MATTER DAMAGE FOLLOWING PEDIATRIC TBI

A4-07 7:15 AM
Moore, Megan; University of Washington
AVAILABILITY OF OUTPATIENT REHABILITATION SERVICES AND BARRIERS TO CARE FOR VULNERABLE POPULATIONS AFTER PEDIATRIC TBI

POSTER SESSION II

BIOMARKER

A5-01 3:00 PM
Bogoslovsky, Tanya; Center for Neuroscience and Regenerative Medicine
SINGLE MOLECULAR ARRAY GLIAL FIBRILLARY ACID PROTEIN AND TOTAL TAU ARE INCREASED UP TO 90 DAYS AFTER TRAUMATIC BRAIN INJURY

A5-02 3:15 PM
Kilbaugh, Todd; University of Pennsylvania
PERIPHERAL BLOOD MITOCHONDRIAL DNA AS A BIOMARKER OF CEREBRAL MITOCHONDRIAL DYSFUNCTION FOLLOWING TRAUMATIC BRAIN INJURY

A5-03 3:30 PM
Rhind, Shawn; DRDC Toronto
ALTERATIONS OF CIRCULATING CHEMOKINES IN RELATION TO NEUROLOGICAL OUTCOME AFTER MODERATE-TO-SEVERE TBI

A5-04 3:45 PM
Thelin, Eric; Karolinska Institutet
NEURON-SPECIFIC ENOLASE IS SIGNIFICANTLY CORRELATED TO OUTCOME POST TRAUMATIC BRAIN INJURY, ALBEIT NOT IN PRESENCE OF SERUM S100B

A5-05 3:00 PM
Wong, Ling; National Intrepid Center of Excellence
TRANSCRANIAL DOPPLER MEASURES EFFECTS OF MIND-BODY TRAINING ON CEREBRAL AUTOREGULATION IN SERVICE MEMBERS WITH COMBAT RELATED TBI

A5-06 3:15 PM
Torch, William; Washoe Sleep Disorders Centers
PROGRESSIVE LIMBIC ANTEROGRADE TRANS-NEURONAL DEGENERATION: A NEUROPATHOLOGICAL & -RADIOLOGICAL BIOMARKER IN HIPPOCAMPAL DISEASE

A5-07 3:30 PM
Samadani, Uzma; New York University School of Medicine
HELMETS MAY PROVIDE PARTIAL PROTECTION AGAINST CONCUSSION: A PROSPECTIVE STUDY WITH SCAT3 AND EYE TRACKING

A5-08 3:45 PM
Gill, Jessica; NIH
PERIPHERAL CONCENTRATIONS OF TOTAL TAU ARE INCREASED IN MILITARY PERSONNEL WHO SUSTAIN TRAUMATIC BRAIN INJURIES DURING DEPLOYMENT

A5-09 3:00 PM
Algamal, Moustafa; Roskamp Institute
EXPLORING THE MOLECULAR OVERLAP IN THE BRAIN AND PLASMA OF TBI AND AD MOUSE MODELS USING PROTEOMIC AND LIPIDOMIC TECHNOLOGY

A5-10 3:15 PM
Tenovuo, Olli; Turku University Hospital
GFAP AND UCH-L1 DURING THE FIRST WEEK AFTER A TBI - CORRELATIONS WITH CLINICAL AND IMAGING FINDINGS AND OUTCOME

A5-11 3:30 PM
Wanner, Ina; UCLA
A NEW PANEL OF HUMAN ASTROGLIAL NEUROTRAUMA BIOMARKERS AND TRAUMA RELEASE MECHANISMS

A5-12 3:45 PM
Griffiths, Daniel; University of Arizona College of Medicine
EVALUATION OF THE EXTRACELLULAR MATRIX AS A SOURCE OF BIOMARKERS FOR INJURY SEVERITY WITHIN 24 HOURS OF DIFFUSE BRAIN INJURY

A5-13 3:00 PM
Wang, Kevin; University of Florida
OPERATION BRAIN TRAUMA THERAPY (OBTT): SERUM-BASED BIOMARKER INVESTIGATION IN A MICROPIG FLUID PERCUSSION INJURY MODEL

A5-14 3:15 PM
Yang, Zhihui; University of Florida
A SYSTEMATIC RAT SPINAL CORD INJURY BIOMARKER STUDY AND TEMPORAL BIOMARKER PROFILING IN TWO BIOFLUID TYPES

A5-15 3:30 PM
Wang, Kevin; University of Florida
HUMAN SPINAL CORD INJURY CSF AND SERUM BIOMARKER STUDY

A5-16 3:45 PM
Sharrock, Matthew; University of Kansas Medical Center
PROTON MAGNETIC RESONANCE SPECTROSCOPY PREDICTORS OF TISSUE LOSS AFTER TRAUMATIC BRAIN INJURY

A5-17 3:00 PM
Hutchison, Michael; University of Toronto
COMPARISON OF SYSTEMIC INFLAMMATORY PROFILES IN HEALTHY ATHLETES WITH AND WITHOUT A HISTORY OF CONCUSSION

A5-18 3:15 PM
Boutte, Angela; Walter Reed Army Institute of Research
MULTIVARIATE BIOMARKER PROFILING, SENSORY MOTOR DEFICITS, CONSCIOUSNESS AFTER SINGLE AND REPEAT PROJECTILE CONCUSSIVE INJURY

A5-19 3:30 PM
Johnson, David; Walter Reed Army Institute of Research
INVESTIGATION OF PUTATIVE ACUTE SERUM DIAGNOSTIC BIOMARKERS IN A PROJECTILE CONCUSSIVE IMPACT INJURY

A5-20 3:45 PM
Deng-Bryant, Ying; Walter Reed Army Institute of Research
DISCOVERING PROGNOSTICATORS FOR REPEATED CONCUSSIONS: A GLOBAL METABOLOMIC STUDY

EDEMA

A6-01 3:00 PM
Atkins, Tyler; Carolinas Medical Center
ACUTE HYDROCEPHALUS IN CERVICAL SPINAL CORD INJURY: TWO DISTINCT PATHOPHYSIOLOGIC CAUSES AND LITERATURE REVIEW

A6-02 3:15 PM
Washington, Patricia; Columbia University
APOE GENOTYPE AND ACUTE EDEMA FORMATION FOLLOWING EXPERIMENTAL TRAUMATIC BRAIN INJURY

A6-03 3:30 PM
Maeda, Takeshi; Nihon University School of Medicine
CILOSTAZOL ATTENUATES BLOOD-BRAIN BARRIER DISRUPTION AND SUBSEQUENT SECONDARY CELLULAR DAMAGE FOLLOWING CORTICAL CONTUSION IN RATS

ENDOCRINE

A7-01 3:45 PM
Thomas, Theresa; University of Arizona College of Medicine
EXPERIMENTAL DIFFUSE BRAIN INJURY LEADS TO CHRONIC CORTICOSTERONE DYSFUNCTION WITH EVIDENCE OF COMPROMISED NEURON MORPHOLOGY

A7-02 3:00 PM
Vanino, Dana; University of Pittsburgh
A PROSPECTIVE EVALUATION OF NEURO-ENDOCRINE AND NUTRITION ABNORMALITIES FOLLOWING SEVERE TRAUMATIC BRAIN INJURY IN ADULT PATIENTS

A7-03 3:15 PM
Mazzeo, Anna Teresa; University of Torino
ENDOCRINE DYSFUNCTION AND PITUITARY AUTOIMMUNITY IN CRITICAL AND NEUROCRITICAL ILLNESS

REGENERATION & PLASTICITY

A8-01 3:30 PM
Rabchevsky, Alexander; UKY
PHARMACOLOGICAL MANIPULATION OF MTOR ACTIVITY TO MODULATE MALADAPTIVE INTRASPINAL PLASTICITY AND AUTONOMIC DYSREFLEXIA

A8-02 3:45 PM
Chen, Jinhui; Indiana University School of Medicine
IN VIVO REPROGRAMMING REACTIVE GLIA INTO IPSCS TO PRODUCE NEW NEURONS IN THE CORTEX FOLLOWING TBI

A8-03 3:00 PM
Wang, Xiaoting; Indiana University School of Medicine
TRAUMATIC BRAIN INJURY SEVERITY AFFECTS NEUROGENESIS IN ADULT MOUSE HIPPOCAMPUS

A8-04 3:15 PM
Costine, Beth; Massachusetts General Hospital/ Harvard Medical School
FIX THE LESION OR KEEP BRAIN DEVELOPMENT GOING? NEUROBLAST PATTERNS AFTER TBI IN THE IMMATURE GYRENCEPHALIC BRAIN

A8-05 3:30 PM
Bergold, Peter; SUNY-Downstate Medical Center
SPECIFIC MODES OF REMYELINATION ARE ASSOCIATED WITH IMPROVED BEHAVIORAL OUTCOMES AFTER CONTROLLED CORTICAL IMPACT

A8-06 3:45 PM
Oswald, Duane; The Ohio State University Medical Center
GOLLI-MYELIN BASIC PROTEIN IS REQUIRED FOR MATURATION OF OLIGODENDROCYTE PROGENITORS AND REMYELINATION OF CONTUSED SPINAL CORDS

A8-07 3:00 PM
Segal, Andrew; UCLA
EXAMINING THE TIME-COURSE OF D-CYCLOSERINE ADMINISTRATION IN DEVELOPING RATS FOLLOWING LATERAL FLUID PERCUSSIVE INJURY

A8-08 3:15 PM
Lemmon, Vance; Univ. of Miami
MIASCI ONLINE: AN ANNOTATION TOOL FOR THE MINIMAL INFORMATION ABOUT A SPINAL CORD INJURY EXPERIMENT (MIASCI) REPORTING STANDARD

A8-09 3:30 PM
Hoffman, Ann; University of California Los Angeles
IMMEDIATE AND PERSISTENT DENDRITIC HYPERTROPHY IN THE BASOLATERAL AMYGDALA FOLLOWING EXPERIMENTAL DIFFUSE TRAUMATIC BRAIN INJURY

A8-10 3:45 PM
Wu, Ping; University of Texas Medical Branch
INDUCED MOTOR NEURON DIFFERENTIATION FROM ENDOGENOUS NEURAL STEM CELLS IN MICE AFTER SPINAL CORD INJURY

A8-11 3:00 PM
Powell, Melissa; Virginia Commonwealth University
INTERACTIVE ROLE OF MATRIX METALLOPROTEINASE 9 AND OSTEOPONTIN IN OLFACTORY BULB SYNAPTOGENESIS FOLLOWING TBI

A8-12 3:15 PM
Vascak, Michal; Virginia Commonwealth University
THE EFFECT OF MILD TRAUMATIC BRAIN INJURY (MTBI) ON THE STRUCTURAL PLASTICITY OF THE AXON INITIAL SEGMENT (AIS)

POSTER SESSION III

AGING

B1-01 4:00 PM
Kinoshita, Takahiro; Osaka General Medical Center
DECOMPRESSIVE CRANIECTOMY IN CONJUNCTION WITH LESION EVACUATION IN GERIATRIC TRAUMATIC BRAIN INJURY: A PROPENSITY SCORE ANALYSIS

B1-02 4:15 PM
Mouzon, Benoit; Roskamp Institute
THE ROLE OF TAU AND OTHER PATHOLOGIES IN AN ANIMAL MODEL OF REPETITIVE MTBI

B1-03 4:30 PM
Lynch, Cillian; Roskamp Institute
CHRONIC IMPAIRMENT OF CEREBRAL BLOOD FLOW IN A MOUSE MODEL OF REPETITIVE MILD TRAUMATIC BRAIN INJURY

B1-04 4:45 PM
Thompson, Hilaire; The Univ. of Washington
AGING RELATED DIFFERENCES IN PATTERNS OF MEDICATION USE AT TIME OF TRAUMATIC BRAIN INJURY

B1-05 4:00 PM
Von Leden, Ramona; USUHS
AGING RATS SHOW ALTERATIONS TO GLIAL CELL ACTIVATION AND FUNCTIONAL RECOVERY AFTER SPINAL CORD INJURY

B1-06 4:15 PM
Harris, Janna; Univ. of Kansas Medical Center
1H-MRS SUGGESTS MECHANISMS UNDERLYING POOR RECOVERY AFTER INJURY TO THE AGED BRAIN

B1-07 4:30 PM
Chou, Austin; University of California - San Francisco
EFFECT OF AGING ON HIPPOCAMPAL-DEPENDENT COGNITION AND NEUROINFLAMMATORY RESPONSES AFTER TRAUMATIC BRAIN INJURY

B1-08 4:45 PM
Bachstetter, Adam; University of Kentucky
MW151, A SMALL MOLECULE INHIBITOR OF NEUROINFLAMMATION, PREVENTS CLOSED HEAD INJURY INDUCED COGNITIVE DEFICITS IN APP/PS1 KI MICE

B1-09 4:00 PM
Isokuortti, Harri; University of Tampere
WHO GETS HEAD TRAUMA OR RECRUITED IN MILD TRAUMATIC BRAIN INJURY RESEARCH?

NEURODEGENERATION

B2-01 4:15 PM
Glushakova, Olena; Banyan Biomarkers, Inc.
THE ROLE OF APOPTOSIS IN LONG-TERM AXONAL, MICROVASCULAR AND BLOOD-BRAIN BARRIER DAMAGE AFTER TRAUMATIC BRAIN INJURY IN RATS

B2-02 4:30 PM
Saber, Maha; Lerner's Research Institute at Cleveland Clinic
THE ROLE OF TREM2 IN TRAUMATIC BRAIN INJURY-INDUCED NEUROINFLAMMATION AND NEURODEGENERATION

B2-03 4:45 PM
Torch, William; Washoe Sleep Disorders Centers
PROGRESSIVE LIMBIC ANTEROGRADE TRANS-NEURONAL DEGENERATION (LATND): A NEUROPATHOLOGICAL BIOMARKER IN TBI-INDUCED CTE & DEMENTIA

B2-04 4:00 PM
Greco, Tiffany; UCLA
EMERGING ROLE OF GAPDH IN TBI INDUCED AMYLOIDOSIS

B2-05 4:15 PM
Dore, Sylvain; University of Florida
HIPPOCAMPAL DEGENERATION AFTER TRAUMATIC BRAIN INJURY: THE ROLES OF THE PGE2 EP1 RECEPTOR

B2-06 4:30 PM
Dixon, C. Edward; University of Pittsburgh
REGIONAL EXPRESSION OF WILD-TYPE ALPHA-SYNUCLEIN AFTER TRAUMATIC BRAIN INJURY IN RATS

B2-07 4:45 PM
Watts, Lora; University of Texas Health Science Center
NEUROPROTECTIVE EFFECT OF METHYLENE BLUE IN MODERATE TRAUMATIC BRAIN INJURY

B2-08 4:00 PM
Kayed, Rakez; University of Texas Medical Branch, Galveston
TOXIC TAU SEEDS DERIVED FROM TRAUMATIC BRAIN INJURY MODELS ACCELERATE COGNITIVE DYSFUNCTION IN TAUOPATHY MICE

B2-09 4:15 PM
Cartagena, Casandra; Walter Reed Army Insitute of Research
ACUTE REGION OF INTEREST CHANGES IN KEY BRAIN INJURY MARKERS FOLLOWING PENETRATING BALLISTIC-LIKE BRAIN INJURY

B2-10 4:30 PM
Boutte, Angela; Walter Reed Army Institute of Research
BRAIN CATHEPSIN B IS ELEVATED IN BOTH MILD-CLOSED AND SEVERE-PENETRATING TRAUMATIC BRAIN INJURY MODELS

B2-11 4:45 PM
Lucke-Wold, Brandon; West Virginia University
MODELING CHRONIC NEURODEGENERATION FOLLOWING NEUROTRAUMA: A MULTIPLE MODEL EXPERIENCE

AXONAL INJURY

B3-01 4:00 PM
Daphalapurkar, Nitin; Johns Hopkins University
DYNAMIC SHEARING DEFORMATIONS IN LIVING HUMAN BRAIN WITH RELEVANCE TO TRAUMATIC BRAIN INJURY

B3-02 4:15 PM
Volman, Vladislav; L-3 Communications
A COMPUTATIONAL MODEL OF WHITE MATTER AXON FOR QUANTIFYING ACUTE AND DELAYED INJURY SEQUELAE, WITH APPLICATION TO REPEATED INJURY

B3-03 4:30 PM
Brizuela, Mariana; University of Tasmania
THE MICROTUBULE-STABILIZING DRUG EPOTHILONE D INCREASES AXONAL SPROUTING RESPONSE IN AN IN VITRO MODEL OF TRANSECTION INJURY

B3-04 4:45 PM
McNally, Shannon; National Institutes of Health
DTI CORRELATES OF ATTENTION AND PROCESSING SPEED IN SUB-ACUTE AND CHRONICTRAUMATIC BRAIN INJURY

B3-05 4:00 PM
Smith, Caleb; Texas Tech University
THERAPEUTIC EFFECTS OF TAMOXIFEN IN SPINAL CORD INJURY

B3-06 4:15 PM
Mayer, Andrew; The Mind Research Network
CROSS-SECTIONAL DIFFERENCES IN FRACTIONAL ANISOTROPY WITHOUT LONGITUDINAL EVIDENCE OF RECOVERY BY ONE MONTH POST-CONCUSSION

B3-07 4:30 PM
Ruven, Carolin; The University of Hong Kong
TRANSPLANTATION OF EMBRYONIC SPINAL CORD DERIVED CELLS INTO TRANSECTED PERIPHERAL NERVE TO PREVENT MUSCULAR ATROPHY

B3-08 4:45 PM
Dolle, Jean-Pierre; University of Pennsylvania
STABILIZING MICROTUBULES AFTER TRAUMATIC AXONAL INJURY MITIGATES ACCUMULATION OF TAU, CALCIUM INFLUX AND AXONAL DEGENERATION

B3-09 4:00 PM
Jacobs, Kimberle; Virginia Commonwealth University
FUNCTIONAL ALTERATIONS IN INTRINSIC AND SYNAPTIC PROPERTIES 1 MONTH AFTER MILD TRAUMATIC BRAIN INJURY

B3-10 4:15 PM
Jin, Xiaotao; Virginia Commonwealth University
ALTERED GABAERGIC SYNAPTIC TRANSMISSION IN LAYER V PYRAMIDAL NEURONS AFTER MILD TRAUMATIC BRAIN INJURY

B3-11 4:30 PM
Gangolli, Mihika; Washington University in St. Louis
ADVANCED DIFFUSION MRI METHODS TO QUANTITATIVELY DISTINGUISH BETWEEN COMPLEX WHITE MATTER AND TRAUMATIC AXONAL INJURY

B3-12 4:45 PM
Zhang, Liying; Wayne State Univ
BLAST INDUCED SPATIAL AND TEMPORAL ALTERATIONS IN GLIAL EXPRESSION AND AXONAL INJURY IN THE RAT SPINAL CORD

B3-13 4:00 PM
Zhang, Liying; Wayne State Univ
OPEN FIELD PRIMARY BLAST EXPOSURE INDUCES NEURONAL AND GLIAL ALTERATIONS IN FRONTAL CORTEX

B3-14 4:15 PM
Zhang, Liying; Wayne State University
BIOMECHANICAL RESPONSE, NEUROPATHOLOGY AND BIOMARKER EXPRESSION IN AN EXPERIMENTAL MODEL OF TRAUMATIC BRAIN INJURY

B3-15 4:30 PM
Catenaccio, Eva; Albert Einstein College of Medicine
NECK STRENGTH IS ASSOCIATED WITH HISTORY OF CONCUSSION IN AMATEUR ADULT SOCCER PLAYERS

EPILEPSY & SEIZURE

B4-01 4:30 PM
Grinberg, Yelena Y.; University of California, Riverside
PROGRESSIVE SEIZURES FOLLOWING MICROGLIAL ACTIVATION AND INFLUX OF PROFESSIONAL APCS IN AUTOIMMUNE TARGETING OF ASTROCYTES

B4-02 4:45 PM
Ritter, Anne; University of Pittsburgh
NEURONAL GLUTAMATE TRANSPORTER GENETIC VARIATION: IMPACT ON EPILEPTOGENESIS AND EPILEPSY RISK FOLLOWING SEVERE TBI

B4-03 4:00 PM
Ritter, Anne; University of Pittsburgh
COMPARISON OF FACTORS PREDICTING POST-TRAUMATIC SEIZURE AT 1, 2, & 5 YEARS POST-INJURY: A TBIMS ANALYSIS

B4-04 4:15 PM
Lu, Xi-Chun May; Walter Reed Army Institute of Research
EFFECTS OF LEVETIRACETAM AND GABAPENTIN COMBINATION THERAPY ON POST-TRAUMATIC NONCONVULSIVE SEIZURES (NCS) INDUCED BY A PENETRATIN

B4-05 4:30 PM
Lu, Xi-Chun; Walter Reed Army Institute of Research
SYNERGISTIC EFFECTS OF PHENYTOIN AND ETHOSUXIMIDE AGAINST POST-TRAUMATIC NONCONVULSIVE SEIZURES

POSTER SESSION IV

FUNCTION

B5-01 4:45 PM
Thompson, Hilaire; The Univ. of Washington
SUICIDAL IDEATION IN THE FIRST 6 MONTHS POST-MILD TBI

B5-02 5:00 PM
Haefeli, Jenny; UCSF Brain and Spinal Injury Center
MONITORING SENSORY FUNCTION AFTER CERVICAL SPINAL CORD INJURY IN NON-HUMAN PRIMATES

B5-03 5:15 PM
Sharma, Sourabh; University of California, San Francisco
OUTPATIENT CARE REFERRAL AT 3-MONTHS IS ASSOCIATED WITH 6-MONTH SYMPTOMATOLOGY FOLLOWING MILD TBI

IMAGING

B6-01 5:30 PM
Levin, Harvey; Baylor College of Medicine
IS DTI A NEUROIMAGING MARKER FOR MTBI WITH LOSS OF CONSCIOUSNESS?

B6-02 5:45 PM
Joshi, Shristi; Center for Neuroscience and Regenerative Medicine
STREAMLINING PARTICIPANT RECRUITMENT FOR TBI AND PTSD RESEARCH STUDIES

B6-03 5:00 PM
Wilson, Colin; Center for Neuroscience and Regenerative Medicine, USUHS
CHARACTERIZATION OF THE CONTROLLED CORTICAL IMPACT BRAIN INJURY MODEL BASED ON LONGITUDINAL MONITORING BY FDG-PET

B6-04 5:15 PM
Williford, Joshua; Center for Neuroscience and Regenerative Medicine/ Henry M. Jackson Foundation
KINETICS OF TRAUMATIC MENINGEAL INJURY USING DYNAMIC CONTRAST ENHANCED FLUID ATTENUATED INVERSION RECOVERY IMAGING

B6-05 5:30 PM
Urbanczyk, Caryn; Duke University
SHEAR SHOCK WAVE DEVELOPMENT IN NEUROLOGICAL TISSUES

B6-06 5:45 PM
Rodgers, Richard; Indiana University School of Medicine
CLINICAL UTILITY OF OUTPATIENT FOLLOW-UP COMPUTED TOMOGRAPHY IN A TRAUMATIC SUBDURAL HEMATOMA POPULATION

B6-07 5:00 PM
Robertson, Courtney; Johns Hopkins School of Medicine
PET IMAGING OF A7 NICOTINIC ACETYLCHOLINE RECEPTORS IN A RAT MODEL OF TRAUMATIC BRAIN INJURY

B6-08 5:15 PM
Whalen, Michael; Massachusetts General Hospital
DECREASED CEREBRAL BLOOD FLOW IS ASSOCIATED WITH WORSE COGNITIVE OUTCOME AFTER REPETITIVE CONCUSSIONS IN MICE

B6-09 5:30 PM
Duhaime, Ann-Christine; Massachusetts General Hospital
MRI FINDINGS IN ACUTE TBI: INTER-RATER RELIABILITY USING NIH COMMON DATA ELEMENTS

B6-10 5:45 PM
Tu, Tsang-Wei; National Institute of Health
IN VIVO GLUCO-CEST MRI DETECTS METABOLIC CRISIS IN MILD TRAUMATIC BRAIN INJURY

B6-11 5:00 PM
Butman, John; NIH
MICROHEMORRHAGE IS NOT FOREVER: CROSS-SECTIONAL ANALYSIS INDICATES RESOLUTION OVER EXTENDED FOLLOW UP INTERVALS

B6-12 5:15 PM
Butman, John; NIH
IMPROVED VISUALIZATION OF SUPERFICIAL HEMORRHAGE IN SUSCEPTIBILITY WEIGHTED IMAGES

B6-13 5:30 PM
Hosomi, Sanae; Osaka University
CHRONIC NEUROINFLAMMATION ANALYSIS AFTER TRAUMATIC BRAIN INJURY USING TSPO-PET AND MRI IN MICE

B6-14 5:45 PM
Luoto, Teemu; Tampere University Hospital
ACUTE TRAUMATIC INTRACRANIAL LESIONS INCREASE THE RISK OF CERVICAL SPINE INJURIES

B6-15 5:00 PM
Dardzinski, Bernard; USUHS
DIFFUSION MR IMAGING REVEALS ABNORMALITIES IN THE CORPUS CALLOSUM AFTER SINGLE TBI VERSUS OVERLYING CORTEX AFTER REPETITIVE TBI

B6-16 5:15 PM
Schneider, Walter; University of Pittsburgh
QUANTITATIVE WHITE MATTER ANALYSIS WITH HIGH DEFINITION FIBER TRACKING PREDICTS NEUROPSYCHOLOGICAL TEST PERFORMANCE IN CHRONIC TBI

B6-17 5:30 PM
Isokuortti, Harri; University of Tampere
THE TYPE AND LOCATION OF INTRACRANIAL ABNORMALITIES FOLLOWING MILD TRAUMATIC BRAIN INJURY

B6-18 5:45 PM
Okonkwo, David; UPMC Presbyterian
PET IMAGING WITH PITTSBURGH COMPOUND B OF AMYLOID DEPOSITION IN WHITE MATTER IN CHRONIC TBI

B6-19 5:00 PM
Dennis, Emily; USC Keck School of Medicine
LONGITUDINAL CHANGES IN REGIONAL BRAIN VOLUME IN PEDIATRIC TBI: PRELIMINARY ANALYSES

B6-20 5:15 PM
Gatson, Joshua; UT Southwestern Medical Center
AMYLOID PLAQUES ARE INCREASED IN THE BRAIN OF TBI SURVIVORS AT 1, 12, AND 24 MONTHS AFTER INJURY

B6-21 5:30 PM
Herrera, Juan; UTHealth Medical School at Houston
DIFFUSION TENSOR IMAGING ANALYSIS OF MILD TBI

B6-22 5:45 PM
Cartagena, Casandra; Walter Reed Army Insitute of Research
ACUTE CHANGES IN FDG PET AFTER SINGLE AND REPEAT MTBI IN RATS CORRELATE WITH CLINICALLY RELEVANT SYMPTOMS OF CONCUSSION

B6-23 5:00 PM
Senseney, Justin; Walter Reed National Military Med. Center
SOFTWARE TOOL FOR LOADING TRAUMATIC BRAIN INJURY NEUROIMAGE DATA INTO AN EXTERNAL REPOSITORY

B6-24 5:15 PM
Senseney, Justin; Walter Reed National Military Med. Center
SHARED NEUROIMAGING DATA OF MILITARY AND BLAST TRAUMATIC BRAIN INJURY USING A DATA SHARING REPOSITORY

B6-25 5:30 PM
Kou, Zhifeng; Wayne State University
CONNECTOME-SCALE ASSESSMENT OF BRAIN NETWORK CONNECTIVITY IN MILD TRAUMATIC BRAIN INJURY

B6-26 5:45 PM
Wiseman, Natalie; Wayne State University
VALIDATION OF DUAL-INJECTION PERFUSION IMAGING: A PILOT STUDY

NEUROPATHOLOGY

B7-01 5:00 PM
McKee, Ann; Boston University
CLINICOPATHOLOGICAL FINDINGS IN 100 FORMER NFL PLAYERS

B7-02 5:15 PM
Goldstein, Lee; Boston University School of Medicine
EARLY CHRONIC TRAUMATIC ENCEPHALOPATHY IN YOUNG ATHLETES AFTER CONCUSSIVE HEAD INJURY AND A MOUSE MODEL OF IMPACT CONCUSSION

B7-03 5:30 PM
Griffin, Allison; CNRM/HJF/NIH
INJECTABLE FIDUCIAL MARKER IN MRI GUIDED PATHOLOGY OF BRAIN INJURY

B7-04 5:45 PM
Ogier, Michael; French Armed Forces Biomedical Research Institute
LONG-TERM COGNITIVE DEFICITS INDUCED BY TRAUMATIC BRAIN INJURY IN RATS ARE EXAGGERATED BY PRE-EXPOSURE TO LIFE-THREATENING STRESS

B7-05 5:00 PM
Karelina, Kate; Ohio State University
NEUROMETABOLIC CONSEQUENCES OF REPEATED TBI

B7-06 5:15 PM
Hylin, Michael; Southern Illinois University
IMPROVEMENTS IN COGNITIVE FUNCTION FOLLOWING TRAUMATIC BRAIN INJURY VIA EIF2A PHOSPHORYLATION AND REDUCTION IN ER STRESS

B7-07 5:30 PM
Namjoshi, Dhananjay; The University of British Columbia
EXPOSURE TO ANABOLIC ANDROGENIC STEROIDS DOES NOT EXACERBATE ACUTE POST-INJURY OUTCOMES IN MICE SUBJECTED TO REPETITIVE CONCUSSION

B7-08 5:45 PM
Leonessa, Fabio; USUHS
EVIDENCE OF BOTH BRAIN AND SPINAL CORD INJURY IN RATS EXPOSED TO EXPLOSIVE-DRIVEN PRIMARY BLAST

B7-09 5:00 PM
Tchantchou, Flaubert; University of Maryland
A RAT MODEL OF UNDERBODY BLAST-INDUCED BRAIN INJURY WITH EVIDENCE OF NEUROBEHAVIORAL DEFICITS, NEURONAL DEATH AND INFLAMMATION

B7-10 5:15 PM
Washington, Patricia; Columbia University
ASSOCIATION BETWEEN APOE GENOTYPE AND NEURODEGENERATIVE PATHOLOGIES AFTER TRAUMATIC BRAIN INJURY

2015 TRAVEL GRANT AWARDEES

Each year, the National Neurotrauma Society provides a limited number of travel grants to enable and encourage attendees to participate in the annual meeting by easing their financial burden. These travel grants are made possible due to grants provided by the National Institutes of Health / National Institute of Neurological Disorders and Stroke, and the Journal of Neurotrauma.

Please join us in congratulating this years' awardees:
(Denotes Student Competition Finalist)*

Brabazon*, Fiona, Uniformed Services University of the Health Sciences
Brizuela, Mariana, University of Tasmania, Australia
Chao, Honglu, Nanjing Medical University, China
Chou, Austin, University of California San Francisco
Daglas, Maria, Monash University, Australia
Gangolli, Mihika, Washington University in St. Louis
Ganpule*, Shailesh, Johns Hopkins
Gupta, Deepak, All India Institute of Medical Sciences, India
Han*, Kihwan, University of Texas at Dallas
Harun, Rashed, University of Pittsburgh
Holleran*, Laurena, Washington University St. Louis
Hong*, James, Toronto Western Research Institute, Canada
Jernberg, Jennifer, Johns Hopkins
Lajud Avila*, Naima, University of Pittsburgh
Leonard, Anna, University of Alabama at Birmingham
Littlejohn, Erica, University of Kentucky
McCutcheon, Victoria, University of Toronto, Canada
Merkel*, Steven, Temple University School of Medicine
Nielson*, Jessica, University of California San Francisco
Ogle*, Sarah, University of Arizona
Powell, Melissa, Virginia Commonwealth University
Russell, Nicholas, Virginia Commonwealth University
Saber, Maha, Lerner's Research Institute at Cleveland Clinic
Schneider, Brandy, Wayne State University School of Medicine
Strain, Misty, Texas A&M University
Tu, Tsang-Wei, National Institute of Health
Turtle, Joel, Texas A&M University
Ulndreaj, Antigona, University of Toronto
Urbanczyk, Caryn, Duke University
Von Leden, Ramona, Uniformed Services University of the Health Sciences
Vonder Haar, Cole, University of British Columbia
Wang, Xiaoting, Indiana University School of Medicine
Wang, Jiaqiong, University of Miami Miller School of Medicine
Wiseman, Natalie, Wayne State University
Wolahan, Stephanie, University of California Los Angeles

POSTER SESSION V

COGNITION

C1-01 7:00 AM
Mu, Weiya; Albert Einstein College of Medicine
SYMPTOMATIC, PSYCHIATRIC, BEHAVIORAL AND COGNITIVE OUTCOMES IN BLAST EXPOSED VETERANS

C1-02 7:15 AM
Catenaccio, Eva; Albert Einstein College of Medicine
GENDER DIFFERENCES IN EXPOSURE TO AND OUTCOMES OF MILD TRAUMATIC BRAIN INJURY IN AMATEUR ADULT SOCCER PLAYERS

C1-03 7:30 AM
Marion, Donald; Defense and Veterans Brain Injury Center
MILITARY DEPLOYMENT INCREASES THE RISK FOR TBI FOLLOWING DEPLOYMENT

C1-04 7:00 AM
Wright, David; Emory University
VERY EARLY ADMINISTRATION OF PROGESTERONE DOES NOT IMPROVE COGNITIVE OUTCOMES IN PATIENTS WITH MODERATE TO SEVERE TBI

C1-05 7:15 AM
Lopez, Katherine; Center for Neuroscience and Regenerative Medicine
NEUROANATOMICAL AND COGNITIVE DIFFERENCES IN MILD TRAUMATIC BRAIN INJURY PATIENTS WITH AND WITHOUT POST-TRAUMATIC STRESS DISORDER

C1-06 7:30 AM
Shenouda, Christian; Center for Neuroscience and Regenerative Medicine
THE EFFECT OF SINGLE VS. MULTIPLE HEAD INJURIES ON BEHAVIORAL AND COGNITIVE OUTCOMES

C1-07 7:00 AM
Pick, Chaim; Tel Aviv University
MICE, TRAUMATIC BRAIN INJURY, AND COGNITIVE EFFECTS OF ENRICHED ENVIRONMENT

C1-08 7:15 AM
Panenka, William; University of British Columbia
TRAUMATIC BRAIN INJURY CORRELATES IN A VULNERABLY HOUSED POPULATION

C1-09 7:30 AM
Vonder Haar, Cole; University of British Columbia
CONTROLLED CORTICAL IMPACT INCREASES COCAINE INTAKE IN RATS: A POTENTIAL ROLE FOR NEUROINFLAMMATION IN ADDICTION

C1-10 7:00 AM
Hoffman, Ann; University of California Los Angeles
STIMULUS-SPECIFIC ENHANCED CONTEXTUAL FEAR LEARNING FOLLOWING LATERAL FLUID PERCUSSION EXPERIMENTAL TRAUMATIC BRAIN INJURY

C1-11 7:15 AM
Yue, John; University of California, San Francisco
APOE-ε4 IS ASSOCIATED WITH DECREASED SIX-MONTH VERBAL MEMORY PERFORMANCE AFTER MILD TBI

C1-12 7:30 AM
Titus, David J; University of Miami
POSITIVE ALLOSTERIC MODULATION OF THE A7 NICOTINIC ACETYLCHOLINE RECEPTOR REVERSES CHRONIC COGNITIVE DEFICITS AFTER TBI

C1-13 7:00 AM
Bramlett, Helen; University of Miami
DOSE-RESPONSE EVALUATION OF KOLLIDON IN THE MIAMI FLUID PERCUSSION MODEL OF TRAUMATIC BRAIN INJURY: AN OBTT CONSORTIUM STUDY

C1-14 7:15 AM
Johnson, Kathia; University of Texas Medical Branch
PERSISTENT BEHAVIORAL DEFICITS IN RATS AFTER MODERATE FLUID-PERCUSSION INJURY

GENE EXPRESSION

C2-01 7:30 AM
Gill, Jessica; National Institutes of Health
MENINGEAL INJURY DETECTED BY CONTRAST ENHANCED FLUID-ATTENUATED INVERSION RECOVERY IMAGES AND DIFFERENTIAL GENE EXPRESSION

C2-02 7:00 AM
Balakathiresan, Nagaraja; USUHS/HJF
A COMPARATIVE STUDY ON SERUM MICRORNA BIOMARKER SIGNATURES OF MILD TRAUMATIC BRAIN INJURY AND POSTTRAUMATIC STRESS DISORDER

C2-03 7:15 AM
Pitkanen, Asla; Univ. of Eastern Finland
TRANSCRIPTOMICS OF AGGRAVATED EPILEPTOGENESIS AND COGNITIVE DECLINE AFTER TBI IN APP/PS1 MOUSE MODEL OF ALZHEIMERÂ´S DISEASE

C2-04 7:30 AM
Fiskum, Gary; Univ. of Maryland, Baltimore
AEROMEDICAL EVACUATION-RELEVANT HYPOBARIA WORSENS TBI IN RATS EXPOSED TO UNDERBODY BLAST-INDUCED HYPERACCELERATION

C2-05 7:00 AM
May, Hazel; University of Arizona
DIFFUSE TRAUMATIC BRAIN INJURY RESULTS IN BIMODAL VARIATION OF SYNAPTIC MARKER EXPRESSION IN THE SOMATOSENSORY CORTEX OVER TIME

C2-06 7:15 AM
Winkler, Ethan; University of California San Francisco
DRD2 C957T POLYMORPHISM IS ASSOCIATED WITH IMPROVED 6-MONTH VERBAL LEARNING FOLLOWING TRAUMATIC BRAIN INJURY

C2-07 7:30 AM
Puccio, Ava; University of Pittsburgh
BRAIN HYPOXIA RESPONSIVE GENE EXPRESSION IN SEVERE TRAUMATIC BRAIN INJURY PATIENTS

C2-08 7:00 AM
Merchant-Borna, Kian; University of Rochester Med. Ctr.
GENOME-WIDE CHANGES IN GENE EXPRESSION FOLLOWING SPORTS-RELATED CONCUSSION

C2-09 7:15 AM
Weisz, Harris; University of Texas Medical Branch
PATHWAY ANALYSIS OF LONG TERM GENOMIC CHANGES AFTER EXPERIMENTAL TBI

C2-10 7:30 AM
Boone, Debbie; University of Texas Medical Branch
PATHWAY ANALYSIS OF NEUROPROTECTIVE DRUG TREATMENT AFTER ACUTE TRAUMATIC BRAIN INJURY

NEUROCRITICAL CARE

C3-01 7:00 AM
Babu, Maya; Mayo Clinic
THE INFLUENCE OF INSURANCE STATUS ON SPINE TRAUMA PATIENT TRANSFERS AT A LEVEL I TRAUMA CENTER WITH A LARGE CATCHMENT AREA

C3-02 7:15 AM
Baronia, Benedicto; Texas Tech University HSC
TREATMENT OF TRAUMATIC NON-CONVEXITY SUBDURAL HEMORRHAGE IS SIMILAR TO TREATMENT OF TRAUMATIC SUBARACHNOID HEMORRHAGE.

C3-03 7:30 AM
Wolahan, Stephanie; UCLA
EARLY NUTRITIONAL THERAPY AND MINIMAL BLOOD GLUCOSE VARIABILITY IMPROVE OUTCOMES AFTER TBI

C3-04 7:00 AM
Wolahan, Stephanie; UCLA
METABOLOMICS OF HUMAN TRAUMATIC BRAIN INJURY

C3-05 7:15 AM
Choi, Phillip; University of Pittsburgh
USE OF ASPIRIN AND P2Y12 RESPONSE ASSAYS IN DETECTING REVERSAL OF PLATELET DYSFUNCTION CAUSED BY ANTIPLATELET AGENTS IN TBI

C3-06 7:30 AM
Bauer, Joshua; University of Pittsburgh
TRANSFUSION REVERSAL OF PRE-MORBID ORAL ASPIRIN USE IS NOT PROTECTIVE AGAINST RADIOGRAPHIC PROGRESSION OF INTRACRANIAL PATHOLOGY

C3-07 7:00 AM
Hawryluk, Gregory; University of Utah
INSIGHTS FROM HIGH FREQUENCY INTRACRANIAL PRESSURE DATA: A TREATMENT THRESHOLD BELOW 20MMHG MAY BE MORE APPROPRIATE

C3-08 7:15 AM
Hawryluk, Gregory; University of Utah
PATIENTS WITH SPINAL CORD INJURIES FAVOR ADMINISTRATION OF METHYLPREDNISOLONE BUT HAVE LITTLE INPUT INTO ITS ADMINISTRATION

C3-09 7:30 AM
D'Aquila, Kathryn; Westchester Medical Center / University of Phoenix
IMPLEMENTATION OF UNIQUE PROCESS FOR CEREBRAL MICRODIALYSIS AT A LEVEL I TRAUMA CENTER

NEUROTOXICITY / NEUROEXCITATION

C4-01 7:00 AM
Kibayashi, Kazuhiko; Tokyo Women's Medical University
NEUROLOGICAL COMPLICATIONS DUE TO A SUBARACHNOID INJECTION OF HYPERTONIC CONTRAST MEDIA IN RAT

C4-02 7:15 AM
Arun, Peethambaran; Walter Reed Army Institute of Research
ALTERED TRYPTOPHAN METABOLISM IN BLAST-INDUCED TRAUMATIC BRAIN INJURY

PAIN

C5-01 7:30 AM
Jernberg, Jennifer; Johns Hopkins
MORPHINE TREATMENT AFTER TBI EXACERBATES COGNITIVE IMPAIRMENTS AND REDUCES NEURONAL SURVIVAL IN A RAT MODEL

C5-02 7:00 AM
Wu, Junfang; University of Maryland, School of Medicine
TRAUMATIC BRAIN INJURY IN MICE INDUCES CHRONIC HYPERESTHESIA

C5-03 7:15 AM
Wu, Junfang; University of Maryland, School of Medicine
CELL CYCLE ACTIVATION CONTRIBUTES TO DEVELOPMENT AND MAINTENANCE OF NEUROPATHIC PAIN FOLLOWING SPINAL CORD INJURY

POSTER SESSION VI

ELECTROPHYSIOLOGY

C6-01 3:00 PM
Vogel III, Edward; Columbia University
DELAYED PRIMARY BLAST-INDUCED ELIMINATION OF LONG-TERM POTENTIATION IN RAT ORGANOTYPIC HIPPOCAMPAL SLICE CULTURES

C6-02 3:15 PM
Andrade, Pedro; UEF
EFFECT TBI ON SLEEP AFTER LATERAL FLUID-PERCUSSION INJURY IN RATS.

C6-03 3:30 PM
Ulyanova, Alexandra; University of Pennsylvania
ELECTROPHYSIOLOGICAL PHENOTYPING OF HUMAN NEURONS IN SLICES AND DISSOCIATED CULTURE

C6-04 3:45 PM
Lu, Xi-Chun May; Walter Reed Army Institute of Research
TIME-COURSE PROFILE OF EEG ABNORMALITY DETECTED BY QEEG POWER SPECTRAL ANALYSIS FOLLOWING A SINGLE CONCUSSIVE BRAIN INJURY IN RATS

INFLAMMATION

C7-01 3:00 PM
Ziebell, Jenna; Barrow Neurological Inst. at Phoenix
MORPHOLOGY ALONE DOES NOT DEFINE THE RANGE OF MICROGLIAL PHENOTYPES AFTER DIFFUSE BRAIN INJURY

C7-02 3:15 PM
Harrison, Jordan; Barrow Neurological Institute
OMEGA-3 DERIVED LIPID MEDIATORS DIFFERENTIALLY IMPACT FUNCTIONAL OUTCOME, SLEEP, AND MICROGLIAL ACTIVATION AFTER EXPERIMENTAL TBI

C7-03 3:30 PM
Rowe, Rachel; Barrow Neurological Institute
POST-TRAUMATIC SLEEP AS A BIOINDICATOR OF INFLAMMATION: NOVEL TNF-R INHIBITORS RESTORE FUNCTION FOLLOWING EXPERIMENTAL TBI

C7-04 3:45 PM
Alvarado-Velez, Melissa; Georgia Institute of Technology
IMMUNE-MODULATORY HYDROGEL CARRIERS FOR STEM CELL THERAPY AFTER TRAUMATIC BRAIN INJURY

C7-05 3:00 PM
Pezzillo, Michael; John D DIngell VA Medical Center/Wayne State University School of Medicine
ANALYSIS OF IBA-1 AND INFLAMMATORY RESPONSE IN YOUNG ADULT MICE AFTER MILD TRAUMATIC BRAIN INJURY

C7-06 3:15 PM
Rasmussen, Lindsey; Johns Hopkins
PERIPHERAL IMMUNE RESPONSE AFTER PEDIATRIC TRAUMATIC BRAIN INJURY IN RABBIT

C7-07 3:30 PM
Zhang, Zhi; Johns Hopkins School of Medicine
NEUROINFLAMMATION IN A RABBIT MODEL OF PEDIATRIC TRAUMATIC BRAIN INJURY

C7-08 3:45 PM
Kokiko-Cochran, Olga; Lerner Research Institute
ACCUMULATING BETA-AMYLOID ALTERS THE POST-INJURY INFLAMMATORY RESPONSE

C7-09 3:00 PM
Daglas, Maria; Monash University
THE ADAPTIVE IMMUNE RESPONSE IN THE BRAIN CORRELATES WITH LONG-TERM NEUROLOGICAL DYSFUNCTION IN A MOUSE MODEL OF TBI

C7-10 3:15 PM
Hinson, Holly; Oregon Health and Science University
INCIDENCE OF EARLY FEVER IN TBI VERSUS MAJOR TRAUMA

C7-11 3:30 PM
Ojo, Joseph; Roskamp Institute
GREY AND WHITE MATTER PATHOBIOLOGY OF A NEWLY DEVELOPED MODEL OF CHRONIC REPETITIVE CONCUSSIVE HEAD INJURY

C7-12 3:45 PM
Bayir, Hulya; Safar Center for Resuscitation Research
COMBINED HEAD INJURY PLUS RADIATION EXPOSURE SHIFTS SYSTEMIC RESPONSE TO IRRADIATION FROM ANTI- TO PRO-INFLAMMATORY

C7-13 3:00 PM
Turtle, Joel; Texas A&M University
NOCICEPTIVE STIMULATION INDUCES CASPASE 1 ACTIVATION FOLLOWING SPINAL CORD INJURY

C7-14 3:15 PM
Shultz, Sandy; The University of Melbourne
TIBIAL FRACTURE EXACERBATES TRAUMATIC BRAIN INJURY OUTCOMES AND INFLAMMATION IN A MOUSE MODEL OF MULTI-TRAUMA

C7-15 3:45 PM
Yauger, Young; USUHS
NADPH OXIDASE 4 INHIBITION REVERSES IRON INDUCED PERTURBATIONS OF REACTIVE OXYGEN SPECIES WITHIN ACTIVATED MICROGLIA

C7-16 3:00 PM
Moritz, Kasey; USUHS
ALTERATIONS OF PROTEASOME DYNAMICS FOLLOWING TRAUMATIC BRAIN INJURY

C7-17 3:15 PM
Wagner, Amy; Univ. of Pittsburgh
MULTIPLE AROMATIZATION MECHANISMS INFLUENCE MORTALITY AND CNS SECONDARY INJURY PROFILES AFTER SEVERE TBI

C7-18 3:30 PM
Wagner, Amy; Univ. of Pittsburgh
SERUM TUMOR NECROSIS FACTOR-A ASSOCIATION WITH MORTALITY SIX MONTHS AFTER TBI: MECHANISTIC RELATIONSHIPS WITH ESTRADIOL

C7-19 3:45 PM
Reddaway, Jack; University of Arizona
ANTI-INFLAMMATORY DRUGS SHIFT PROPORTIONS OF ACTIVATED MICROGLIA FOLLOWING EXPERIMENTAL DIFFUSE BRAIN INJURY

C7-20 3:00 PM
Lee, Sangmi; University of California San Francisco
P75NTR MEDIATES SYSTEMIC INFLAMMATORY RESPONSES BY MODULATING DIFFERENTIATION OF MYELOID CELLS

C7-21 3:30 PM
Morganti, Josh; University of California San Francisco
SIMULTANEOUS EXPRESSION OF M1/M2 MACROPHAGE POLARIZATION PHENOTYPES FOLLOWING TBI

C7-22 3:15 PM
Loane, David; University of Maryland, School of Medicine
NOX2 REGULATION OF MICROGLIAL ACTIVATION IN THE TBI BRAIN: A NOVEL MECHANISM FOR NEUROPROTECTION AND POST-TRAUMATIC REPAIR

C7-23 3:30 PM
Wilson, Nicole; University of Miami
PHOSPHODIESTERASE 4B INHIBITION AS AN ANTI-INFLAMMATORY TREATMENT FOR TRAUMATIC BRAIN INJURY

C7-24 3:45 PM
Ulndreaj, Antigona; University of Toronto
ANTIBODY-MEDIATED AUTOIMMUNITY AFTER CERVICAL SPINAL CORD INJURY: DISTINCT ROLES FOR IGG AND IGM

C7-25 3:00 PM
DeMar, James; Walter Reed Army Institute of Research
EVALUATION OF POLYUNSATURATED FATTY ACID DERIVED MEDIATORS OF INFLAMMATION TO AMELIORATE PRIMARY BLAST WAVE INJURIES IN RATS

C7-26 3:15 PM
Johnson, David; Walter Reed Army Institute of Research
ACUTE AND SUBACUTE MICRORNA MODULATION FOLLOWING PBBI

C7-27 3:30 PM
Wang, Ying; Walter Reed Army Institute of Research
CCL2 LEVELS IN CSF AND ITS CORRELATION WITH BLAST-INDUCED NEUROTRAUMA IN RATS

C7-28 3:45 PM
Boutte, Angela; Walter Reed Army Institute of Research
HYPOXEMIA AND HEMORRHAGIC SHOCK DELAY INFLAMMATION AND GFAP-DEGRADATION IN RAT PENETRATING BALLISTIC-LIKE BRAIN INJURY.

C7-29 3:00 PM
Madathil, Sindhu; Walter Reed Army Institute of Research
TEMPORAL AND REGIONAL CHANGES IN MICROGLIAL PROLIFERATION FOLLOWING PENETRATING BALLISTIC-LIKE BRAIN INJURY IN RATS

INTRACRANIAL PRESSURE

C8-01 3:15 PM
Rodgers, Richard; Indiana University School of Medicine
THE EFFECT OF OSMOTIC AGENTS ON CEREBRAL MICROCIRCULATION AFTER TRAUMATIC BRAIN INJURY

C8-02 3:30 PM
Armonda, Rocco; MedStar-Washington Hospital Center/Georgetown University Hospital
RAUMEDIC BOLT: INITIAL CLINICAL EXPERIENCE IN A NEUROSURGICAL POPULATION

NEUROTRANSMITTER

C9-01 3:45 PM
Harun, Rashed; University of Pittsburgh
SEX HORMONE STATUS AND CONTROLLED CORTICAL IMPACT AFFECT DOPAMINE NEUROTRANSMISSION AND RESPONSE TO METHYLPHENIDATE ADMINISTRATION

C9-02 3:00 PM
Myrga, John; University of Pittsburgh
DOPAMINE SYSTEM GENETICS AND SEX INTERACT TO AFFECT COGNITIVE DYSFUNCTION AFTER TBI

C9-03 3:15 PM
Carlson, Shaun; University of Pittsburgh
ADMINISTRATION OF LITHIUM IMPROVES NEUROTRANSMISSION AND INCREASES VESICULAR DOCKING PROTEINS IN THE STRIATUM AFTER CCI

C9-04 3:30 PM
Schneider, Brandy; Wayne State University
TRAUMATIC BRAIN INJURY PRECEDES ENHANCED FEAR CONDITIONING AND SUBREGIONAL CHANGES IN HIPPOCAMPAL EXCITATORY/INHIBITORY TONE

POSTER SESSION VII

BIOENGINEERING

D1-01 4:00 PM
Stemper, Brian; Medical College of Wisconsin
SUBCONCUSSIVE HEAD IMPACT HISTORY FOR CONCUSSED AND NON-CONCUSSED COLLEGE FOOTBALL PLAYERS

D1-02 4:15 PM
Stemper, Brian; Medical College of Wisconsin
SEX-BASED BEHAVIORAL DIFFERENCES IN RATS FOLLOWING HEAD ROTATIONAL ACCELERATION INJURY

D1-03 4:30 PM
Hicks, Ramona; One Mind
CREATING A KNOWLEDGE NETWORK FOR TBI RESEARCH: THE ONE MIND PORTAL

D1-04 4:45 PM
Race, Nick; Purdue University/Indiana University
EXPLORING THE LINKS BETWEEN BLAST-INDUCED TRAUMATIC BRAIN INJURIES AND PSYCHOSOCIAL DEFICITS IN RATS

MODELING

D2-01 4:00 PM
Wirth, Peter; Colby College
MILD TRAUMATIC BRAIN INJURY IN MALE AND FEMALE RATS: CHARACTERIZATION OF A NEW INJURY PARADIGM

D2-02 4:15 PM
Jamnia, Naseem; DePaul University
CLOSED-HEAD SINGLE AND REPEAT CONTROLLED CORTICAL IMPACT IN THE ADULT RAT: EFFECTS ON BEHAVIOR, PHYSIOLOGY, AND PATHOLOGY

D2-03 4:30 PM
Cui, Jianxia; L-3 communications/Applied Technologies
A COMPUTATIONAL MODEL OF CORTICAL NETWORK FOR QUANTIFYING NEUROBEHAVIORAL SEQUELAE OF CONCUSSION LINKED TO TRAUMATIC AXONAL INJURY

D2-04 4:45 PM
Ferguson, Scott; Roskamp Institute
VISUAL DYSFUNCTION SCREENING IN MICE AFTER TBI USING AN OPTOMOTOR ASSESSMENT OF THE OPTOKINETIC RESPONSE

D2-05 4:00 PM
Tenovuo, Olli; Turku University Hospital
INJURY PROFILES, DEMOGRAPHY AND REPRESENTATIVENESS OF PATIENTS WITH TBI ATTENDING A REGIONAL EMERGENCY DEPARTMENT

D2-06 4:15 PM
Ponnaluri, Aditya; UCLA
ANALYZING CONCUSSION SCORE CRITERIA FOR VINYL NITRILE FOAM AND MICROLATTICE MATERIAL USING A ONE-DIMENSIONAL MODEL

D2-07 4:30 PM
Tucker, Laura; USUHS
A SINGLE CONCUSSIVE BRAIN INJURY TRANSIENTLY DISRUPTS HOME CAGE ACTIVITIES IN MALE AND FEMALE C57BL/6J MICE

D2-08 4:45 PM
Leonard, Anna; University of Alabama at Birmingham
LOCALIZATION OF THE CORTICOSPINAL TRACT IN PIGS: IMPLICATIONS FOR MODELLING TRAUMATIC SPINAL CORD INJURY

D2-09 4:00 PM
Martens, Kris; University of British Columbia
BIOMECHANICAL AND FUNCTIONAL CHARACTERIZATION OF CHIMERA IN AN APP/PS1 MODEL OF ALZHEIMER'S DISEASE

D2-10 4:15 PM
Abboud, Andrew; University of Pittsburgh
DYNAMIC PROFILING: OUTCOME PREDICTION IN TBI BASED ON DEMOGRAPHICS, INJURY CHARACTERISTICS, AND INFLAMMATORY MEDIATORS

D2-11 4:30 PM
Abboud, Andrew; University of Pittsburgh
DIFFERENTIAL DYNAMIC NETWORKS OF INFLAMMATION IN CEREBROSPINAL FLUID OF TRAUMATIC BRAIN INJURY SEGREGATE SURVIVORS & NON-SURVIVORS

D2-12 4:45 PM
McCutcheon, Victoria; University of Toronto
DEVELOPMENT AND CHARACTERIZATION OF A ZEBRAFISH MODEL OF TBI

D2-13 4:00 PM
Meconi, Alicia; University of Victoria
IMMUNE CELL ACTIVATION UNDERLYING LEARNING AND MEMORY IMPAIRMENT IN THE JUVENILE FEMALE RAT AFTER REPEAT CLOSED HEAD INJURY

D2-14 4:15 PM
Zhang, Liying; Wayne State University
MECHANICAL RESPONSE OF SWINE EXPOSED TO FREE-FIELD BLASTS

NEUROTRANSPLANTATION

D3-01 4:30 PM
Gajavelli, Shyam; University of Miami
SURVIVAL AND BIODISTRIBUTION OF HUMAN FETAL NEURAL STEM CELL TRANSPLANTS IN PENETRATING BALLISTIC BRAIN INJURY (PBBI)

D3-02 4:45 PM
Cao, Qi Lin; UT Medical School at Houston
TRANSPLANTATION OF HUMAN INDUCIBLE PLURIPOTENT STEM CELL-DERIVED NEURAL STEM CELLS PROMOTES LOCOMOTOR RECOVERY AFTER SCI

TRANSPLANTATION

D4-01 4:15 PM
Armstrong, Regina; USUHS
INTRACEREBROVENTRICULAR TRANSPLANTATION OF ADULT NEURAL STEM CELLS (NSCS) AFTER TBI: PROOF-OF-CONCEPT FOR ACTIVATION OF HOST NSCS

D4-02 4:00 PM
Ahmed, Aminul; University of Miami
DIFFERENTIATION OF FDA-APPROVED HUMAN NEURAL STEM CELLS WITH FUNCTIONAL IMPROVEMENT AFTER A PENETRATING TBI

MONITORING

D5-01 4:30 PM
Gupta, Deepak; AIIMS (All India Institute of Medical Sciences)
CAN CEREBRAL MICRODIALYSIS USEFULNESS BE EXTRAPOLATED TO CLINICAL PROGNOSTICATION ASSESSMENT IN SEVERE TRAUMATIC BRAIN INJURY?

D5-02 4:45 PM
LaPlaca, Michelle; Georgia Institute of Technology/ Emory University
DETECT: A NOVEL TOOL FOR FIELD ASSESSMENT OF CONCUSSION

D5-03 4:00 PM
Kiderman, Alexander; Neuro Kinetics, Inc.
TEST-RETEST REPEATABILITY AND REPRODUCIBILITY OF MULTI-MODAL TESTING IN 3D HEAD MOUNTED DISPLAY (HMD) WITH EYE TRACKING SYSTEM.

D5-04 4:15 PM
Hoffer, Michael; University of Miami
NEUROSENSORY SYMPTOMS COMPLEXES AFTER ACUTE MILD TRAUMATIC BRAIN INJURY

D5-05 4:30 PM
Wang, Jiaqiong; University of Miami
CONDITIONED LOCOMOTION FOLLOWING THORACIC SCI IN RATS: COMPARATIVE ASSESSMENT OF GAIT ANALYSIS USING AUTOMATED DEVICES

D5-06 4:45 PM
Krasberg, Mark; University of New Mexico
RELATIONSHIP OF SIMULTANEOUSLY RECORDED VENTRICULAR AND PARENCHYMAL INTRACRANIAL PRESSURE

D5-07 4:00 PM
Carr, Walter; Walter Reed Army Institute of Research
SYMPTOMOLOGY OBSERVED IN HUMANS FOLLOWING ACUTE EXPOSURE TO EXPLOSIVE BLAST

REHABILITATION

D6-01 4:15 PM
Yu, Mingkun; Shanghai Changzheng Hospital
SPONTANEOUS FRACTURE OF CRANIOPLASTIC TITANIUM IMPLANTS WITHOUT HEAD TRAUMA IN AN ADULT: A CASE STUDY

D6-02 4:30 PM
Strain, Misty; Texas A&M University
EXAMINATION OF STEPPING AND TAIL OSCILLATIONS AS A RESULT OF TEMPORAL RELATIONS AND FREQUENCY

D6-03 4:45 PM
Larson-Dupuis, Camille; Universite de Montreal
IMPACT OF AEROBIC EXERCISE ON COGNITIVE FUNCTIONS IN AN AGING MILD TRAUMATIC BRAIN INJURY POPULATION: A PILOT STUDY

D6-04 4:00 PM
Hamzah, Norhamizan; University Malaya
EFFECT OF COGNITIVE REHABILITATION IN IMPROVING COGNITIVE SYMPTOMS AND DIFFUSION TENSOR IMAGING FINDINGS FOLLOWING MILD TBI

D6-05 4:15 PM
Panenka, William; University of British Columbia
SYMPTOM ATTRIBUTION AFTER MILD TRAUMATIC BRAIN INJURY

D6-06 4:30 PM
Yue, John; University of California, San Francisco
TEMPORAL PROFILE OF CARE FOLLOWING MILD TRAUMATIC BRAIN INJURY: PREDICTORS TO HOSPITAL ADMISSION, OUTPATIENT REFERRAL AND OUTCOME

D6-07 4:45 PM
Kline, Anthony; University of Pittsburgh
OPTIMIZING ENVIRONMENTAL ENRICHMENT TO MODEL PRECLINICAL NEUROREHABILITATION

D6-08 4:00 PM
Temkin, Nancy; University of Washington
TELEPHONE PROBLEM SOLVING TREATMENT FOR ACTIVE DUTY SERVICE MEMBERS WITH MILD TRAUMATIC BRAIN INJURY: A RANDOMIZED CONTROLLED TRIAL

D6-09 4:15 PM
Peduzzi Nelson, Jean; Wayne State University School of Medicine
BRAIN-INITIATED EXERCISE PROGRAM PROMOTES GREATEST RECOVERY AFTER SCI

POSTER SESSION VIII

ASTROCYTE

D7-01 5:00 PM
Hong, Sue; Ann & Robert H. Lurie Children's Hospital
THROMBIN PHOSPHORYLATES MYOSIN LIGHT CHAIN IN ASTROCYTES VIA THE RHO KINASE PATHWAY

D7-02 5:15 PM
Levine, Jaclynn; University of California Los Angeles
TRAUMATICALLY INJURED ASTROCYTES RELEASE A PROTEOMIC SIGNATURE MODULATED BY STAT3 DEPENDENT CELL SURVIVAL

NEUROPROTECTION

D8-01 *withdrawn*

D8-02 5:45 PM
Garcia, Roberto; Baylor College of Medicine
NEUROPROTECTION WITH PEG-HYDROPHILIC CARBON CLUSTERS IN MILD TRAUMATIC BRAIN INJURY COMPLICATED BY HYPOTENSION IN RODENTS

D8-03 5:00 PM
Cherian, Leela; Baylor College of Medicine
NEUROPROTECTIVE EFFICACY OF ERYTHROPOIETIN-MIMETIC PEPTIDE (ARA290) WITH DELAYED ADMINISTRATION AFTER CORTICAL IMPACT INJURY

D8-04 5:15 PM
Husan, Ammar; Baylor College of Medicine
LITHIUM AND VALPROATE ADMINISTRATION PROVIDES NEUROPROTECTION AFTER MILD TRAUMATIC BRAIN INJURY COMPLICATED BY HYPOTENSION

D8-05 5:30 PM
Hoffer, Barry; Case Western Reserve University
LOWERING TUMOR NECROSIS FACTOR-A SYNTHESIS AMELIORATES NEURONAL AND COGNITIVE LOSS AFTER MILD TRAUMATIC BRAIN INJURY IN MICE

D8-06 5:45 PM
Layer, Richard; InVivo Therapeutics
BIODEGRADABLE NEURO-SPINAL SCAFFOLD PRESERVES SPINAL CORD ARCHITECTURE FOLLOWING SPINAL CONTUSION INJURY IN RATS

D8-07 5:00 PM
Hanna, George; Loma Linda University Health
HYPERTONIC SALINE THERAPY AND DECOMPRESSIVE SURGERY WITH MULTI-MODAL THERAPY IN ACUTE SPINAL CORD INJURY

D8-08 5:15 PM
Chavko, Mikulas; Naval Medical Research Center
PROTECTIVE EFFECT OF N- ACETYLCYSTEINE AMIDE (NACA) AGAINST BRAIN DAMAGE AFTER EXPOSURE TO BLAST IN A RAT MODEL

D8-09 5:30 PM
Finan, John; North Shore University Health System
THE EFFECT OF INTERNAL JUGULAR VEIN COMPRESSION ON HEMORRHAGE IN A PORCINE CONTROLLED CORTICAL INJURY MODEL

D8-10 5:45 PM
Choo, Anthony; PsychoGenics Inc.
THE EFFICACY OF PROGESTERONE DEPENDS ON THE TRAUMATIC BRAIN INJURY MODEL

D8-11 5:00 PM
Sutton, Richard; UCLA
TBI-INDUCED METABOLOMIC PROFILES IN ENERGETIC, OXIDATIVE STRESS AND INFLAMMATORY PATHWAYS ARE IMPROVED BY ETHYL PYRUVATE TREATMENT

D8-12 5:15 PM
Geddes, James; University of Kentucky
SELENIUM DEFICIENCY IS DETRIMENTAL TO MITOCHONDRIAL RESPIRATION FOLLOWING TRAUMATIC BRAIN INJURY

D8-13 5:30 PM
Littlejohn, Erica; University of Kentucky
INSULIN-LIKE GROWTH FACTOR-1 OVEREXPRESSION PROMOTES SURVIVAL OF ADULT-BORN NEURONS AFTER TRAUMATIC BRAIN INJURY

D8-14 5:45 PM
Patel, Samirkumar; University of Kentucky
SYNERGISTIC EFFECTS OF B-HYDROXYBUTYRATE AND ACETYL-L-CARNITINE ON MITOCHONDRIAL FUNCTION AFTER SPINAL CORD INJURY

D8-15 5:00 PM
Cebak, John; University of Kentucky
RE-PURPOSING AN FDA-APPROVED DRUG AS AN ANTI-OXIDANT TO SCAVENGE REACTIVE CARBONYLS FOLLOWING TBI-INDUCED LIPID PEROXIDATION

D8-16 5:15 PM
Mondello, Stefania; University of Messina
BIOMARKER PROFILES SUPPORT A NEUROPROTECTIVE EFFECT OF LEVETIRACETAM IN TBI: FINDINGS FROM OPERATION BRAIN TRAUMA THERAPY

D8-17 5:30 PM
Dietrich, W. Dalton; University of Miami Miller School of Medicine
EVALUATION OF GLIBENCLAMIDE IN THE MIAMI FLUID PERCUSSION MODEL OF TRAUMATIC BRAIN INJURY: AN OBTT CONSORTIUM STUDY

D8-18 5:45 PM
Jha, Ruchira; University of Pittsburgh
EVALUATION OF GLIBENCLAMIDE IN THE PITTSBURGH CONTROLLED CORTICAL IMPACT MODEL OF TRAUMATIC BRAIN INJURY: AN OBTT CONSORTIUM STUDY

D8-19 5:00 PM
Dixon, C. Edward; University of Pittsburgh
EVALUATION OF KOLLIDON VA-64 IN THE CONTROLLED CORTICAL IMPACT MODEL OF TRAUMATIC BRAIN INJURY: AN OBTT CONSORTIUM STUDY

D8-20 5:15 PM
Hawkins, Bridget; University of Texas Medical Branch (UTMB)
TAU OLIGOMER SPECIFIC MONOCLONAL ANTIBODY TO TREAT TRAUMATIC BRAIN INJURY

D8-21 5:30 PM
Micci, Maria-Adelaide; University of Texas Medical Branch (UTMB)
THERAPEUTIC APPLICATION OF A PULSED LASER SYSTEM FOR BRAIN TRAUMA.

D8-22 5:45 PM
Harper, Matthew; VA Health Care System; University of Iowa
FUNCTIONAL PRESERVATION OF RETINAL GANGLION CELLS WITH P7C3-S243 FOLLOWING BLAST MEDIATED TBI

D8-23 5:00 PM
Caudle, Krista; Walter Reed Army Institute of Research
EVALUATION OF KOLLIDON VA64 IN THE WRAIR PBBI MODEL: STUDIES FROM THE OPERATION BRAIN TRAUMA THERAPY (OBTT) CONSORTIUM

D8-24 5:15 PM
Mountney, Andrea; Walter Reed Army Institute of Research
THE EFFECTS OF SLEEP-ALTERING DRUGS ON SLEEP ARCHITECTURE RELATIVE TO TRAUMATIC BRAIN INJURY IN RATS

D8-25 5:30 PM
Leung, Lai Yee; Walter Reed Army Institute of Research
SELECTIVE BRAIN COOLING REDUCES MOTOR DEFICITS INDUCED BY COMBINED TRAUMATIC BRAIN INJURY, HYPOXEMIA AND HEMORRHAGIC SHOCK

D8-26 5:45 PM
Deng-Bryant, Ying; Walter Reed Army Institute of Research
EVALUATION OF GLIBENCLAMIDE IN THE WRAIR PBBI MODEL: STUDIES FROM THE OPERATION BRAIN TRAUMA THERAPY (OBTT) CONSORTIUM

VASCULAR

D9-01 5:00 PM
Bond, Lisa; BioAxone BioSciences, Inc.
DEVELOPMENT OF ROCK2-SELECTIVE BA-1049 FOR TREATMENT OF CEREBRAL CAVERNOUS MALFORMATIONS

D9-02 5:15 PM
Park, Eugene; St. Michael
HUMAN UMBILICAL CORD PERIVASCULAR CELL (HUCPVC) THERAPY FOR TRAUMATIC BRAIN INJURY: TARGETING THE NEUROVASCULAR UNIT.

D9-03 5:30 PM
Decker, Matt; University of Florida
INSTITUTIONAL REVIEW OF SCREENING FOR BLUNT CEREBROVASCULAR INJURIES

D9-04 5:45 PM
Bolding, Ian; University of Texas - Medical Branch
A COMPARISON OF THE CEREBRAL VASCULAR EFFECTS OF VANDENBERG OR ADVANCED BLAST SIMULATOR BLAST INJURY IN RATS

D9-05 5:00 PM
Rodriguez, Uylissa; University of Texas Medical Branch
THE EFFECTS OF BLAST-INDUCED NEUROTRAUMA ON CEREBRAL VASCULAR, HISTOPATHOLOGICAL AND BEHAVIORAL OUTCOMES

D9-06 5:15 PM
Hawkins, Bridget; University of Texas Medical Branch
TREATMENT WITH DENDRO[60]FULLERENE PRESERVES NEURONS AFTER TRAUMATIC BRAIN INJURY BUT DOES NOT IMPROVE CEREBRAL VASCULAR RESPONSE

D9-07 5:30 PM
Di Battista, Alex; University of Toronto
PERIPHERAL BLOOD MARKERS OF VASCULAR INJURY IN MODERATE-TO-SEVERE TBI - RELATIONSHIP TO SYSTEMIC CATECHOLAMINES AND OUTCOME.

D9-08 5:45 PM
Kenney, Kimbra; USUHS
FUNCTIONAL NEAR INFRARED SPECTROSCOPY (FNIRS)- 2 NON-INVASIVE METHODS TO ASSESS TRAUMATIC VASCULAR INJURY AFTER TBI

D9-09 5:00 PM
Russell, Nicholas; Virginia Commonwealth University
HEME OXYGENASE-1 AND LIPOCALIN-2 INTERACTION DURING HEME PROCESSING AFTER TRAUMATIC BRAIN INJURY

D9-10 5:15 PM
Kummer, Terrance; Washington University
AXONAL INJURY AND NEUROBEHAVIORAL IMPAIRMENT AFTER SUBARACHNOID HEMORRHAGE

AWARDS CEREMONY

Please join us on Wednesday, July 1st for the Awards Ceremony, where we will honor all poster finalists, WiNTR VISA award winner, and announce the final winners of the:

Michael Goldberger Award
Murray Goldstein Award
Women in Neurotrauma Research Award
Alan Faden Award
Anthony Marmarou Award
AANS/CNS Cranial Trauma Award
AANS/CNS Spinal Trauma Award

WiNTR Women In Neurotrauma Research — Visiting International Scholar Award

The Women in Neurotrauma Research Visiting International Scholar Award (WiNTR-VISA) was established to promote international networking opportunities, and to advance the early careers of women neurotrauma researchers. The Award provides an opportunity for international collaboration by subsidizing both travel to the National Neurotrauma Symposium and a brief period of research training/collaboration in a sponsor's laboratory.

The winner for 2015 is **Ms. Patricia Barra de la Tremblaye**, PhD candidate in the laboratory of Dr. Hélène Plamondon, PhD at the University of Ottawa. In addition to attending the upcoming 33rd Annual NNS Symposium in Santa Fe, Ms. B. de la Tremblaye will participate in on-site collaborative research at the University of Pittsburgh, in the neurotrauma research laboratory of Dr. Anthony Kline, PhD.

The award will be officially recognized during the NNS Awards Ceremony on Wednesday, July 1st. Please join us to congratulate Ms. Patricia B. de la Tremblaye on this achievement!

CME & Disclosure Information

Disclosure of Conflicts

The following speakers, chairs, presenting authors and/or Program Committee members report the following relevant relationships:

Speakers Bureau:

Bansal, Vishal
Consultant: Oxeia Biopharmaceuticals

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Borlongan, Cesar
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Shareholder: Sanbio Inc.

Dhall, Sanjay
Honorarium Recipient:
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Globus Spine

Dietrich, W. Dalton
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Gioia, Gerard
Royalty Recipient: Psychological Assessment Resources, Inc.

Kannan, Sujatha
Holder of Intellectual Property Rights: Glia Therapeutics

Kiderman, Alexander
Employee: Neuro Kinetics, Inc.

Kochanek, Patrick
Holder of Intellectual Property Rights: Patent No.# US 8,628,512 B2
Grant Recipient: NIH and US Army

Kwon, Brian
Advisor/Review Panel: Acorda Therapeutics

Layer, Richard
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Morioka, Kazuhito
Grant Recipient:
NIH (NS088475, NS067092)
Craig H. Neilsen Foundation
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Continuing Medical Education

This activity has been planned and implemented in accordance with the accreditation statement and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of University Health Services Professional Education Programs (UHS-PEP) of Virginia Commonwealth University Health System and the National Neurotrama Society. UHS-PEP is accredited by the ACCME to provide continuing medical education for physicians.

UHS-PEP designates this live activity for a maximum of 31.5 AMA PRA Category 1 Credits(TM) Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Credits are designated as follows:
- UHS-PEP designates a maximum of 23.25 CME credits for the National Neurotrauma Society sponsored portion of the entire symposium.
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I. Describe injury models and novel approaches to study traumatic brain and spinal cord injury.

II. Identify advances in therapeutic targeting to enhance outcome after central nervous system injury.

III. Discuss controversial issues in the translation of therapeutic treatments from the laboratory to the clinic.

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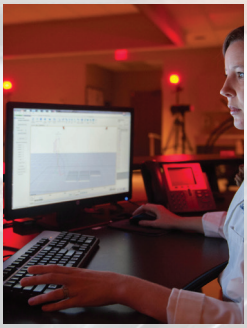


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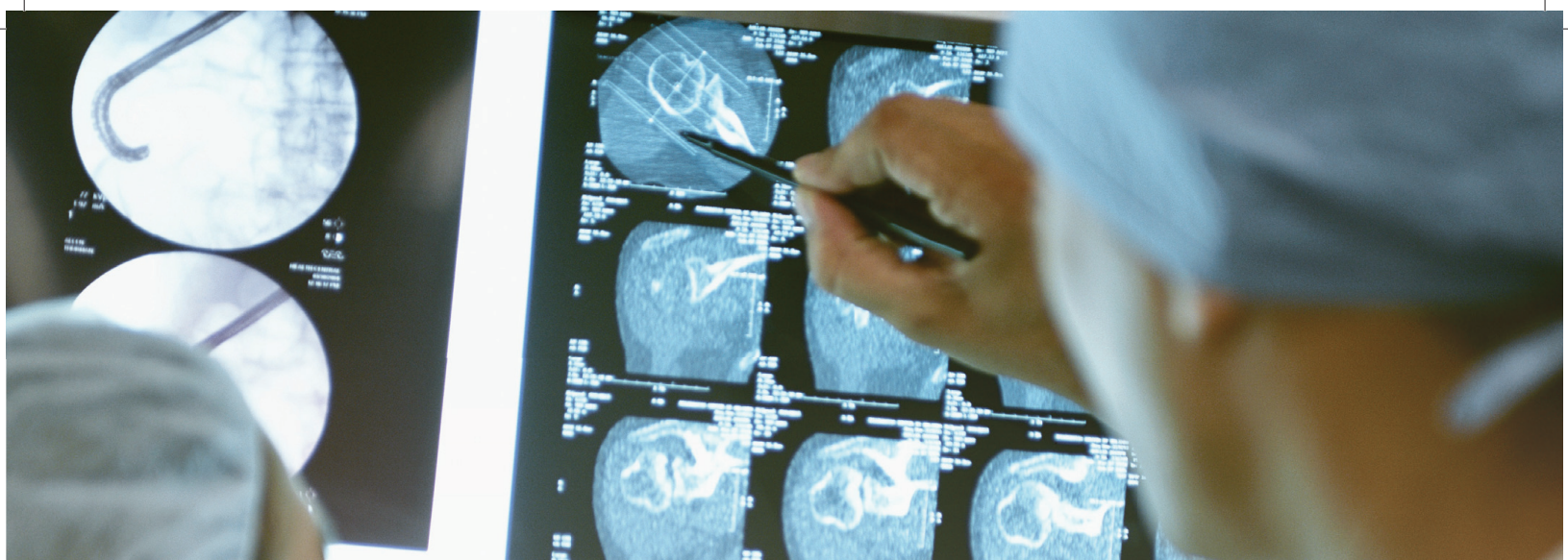

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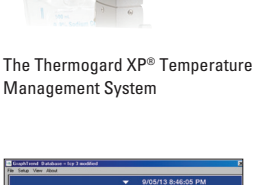

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T1-01

EARLY HINDLIMB UNLOADING PRODUCES CHRONIC BIOMECHANICAL, PHYSIOLOGICAL AND MOLECULAR SIGNATURES OF MALADAPTIVE PLASTICITY IN SCI

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Appropriate limb loading is essential for neurorehabilitation after SCI, in part, because it guides spinal cord neuroplasticity. Complete unloading such as prolonged bed rest may interfere with functional recovery, whereas appropriate afferent information through rehabilitation may improve function by modulating spinal plasticity. The impact of limb loading on synaptic plasticity in SCI remains poorly understood. We investigated long-term biological, biomechanical and physiological consequence of hindlimb unloading (HU) in the acute phase of SCI. Adult female SD rats received a mild SCI (T9; 50 kdyn, IH). Three days post-injury, subjects were randomized to two experimental groups: 1) HU by tail suspension, or 2) normal-loading control. After two weeks, the HU group was returned to normal loading condition. Animals were monitored until 8 weeks post-injury. Assessments included: 1) BBB locomotor recovery; 2) kinematic gait analysis; 3) electrophysiological H-reflex testing at 8 weeks-post injury; 4) spinal cord tissue analysis using biomolecular and robotic confocal microscopy assessments of plasticity-related changes in ventral motorneurons. Results indicated that: 1) HU early after SCI impaired recovery of coordinated gait characteristics and produced excessive excitation of spinal reflex circuits; 2) Chronically increased synaptic glutamate AMPA receptors on the plasma membrane of spinal motor neurons providing a cellular mechanism. Our findings suggest that limb unloading early after SCI induces maladaptive spinal cord plasticity that persists to impair functional recovery in chronic phase, providing a novel mechanistic target for early intervention after SCI to enhance the effect of rehabilitation in the chronic phase following injury.

This works was supported by NS088475, NS067092, Wings for Life Spinal Cord Research Foundation, Craig H. Neilsen Foundation.

Keywords: AMPA, Synaptic Plasticity, Loading, Rehabilitation

T1-02

DENDRITIC MORPHOLOGY AND NEUROTRANSMITTER TYPE OF THORACIC DESCENDING PROPRIOSPINAL NEURONS IN SHAM, AXOTOMY, AND GDNF TREATMENT

Lingxiao Deng[1], Yiwen Ruan[1], Chen Chen[1], Christian Corbin Frye[1], Dale Sengelaub[1], Wenhui Xiong[1], Xiaoming Jin[1], Xiao-Ming Xu[1]

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After spinal cord injury, descending propriospinal neurons (DPSNs) greatly contributed to spontaneous functional recoveries. However, little is known regarding their normal dendritic morphology and plasticity after injury. We applied a G-mutated rabies virus (G-Rabies virus) co-expressing green fluorescence protein (GFP) to reveal Golgi-like dendritic morphology of DPSNs, and their response to axotomy and glial derived neurotrophic factor (GDNF) treatment. We also investigated their neurotransmitter type. The animals were divided into three groups: sham or spinal transection injuries (with or without GDNF). Each group was further divided into injection subgroup A (Fluorescence Gold, FG) and B (G-Rabies virus), with injection into the 2nd lumbar cord. Three days post-injection, transection was performed at the 11th thoracic level, with gelfoam containing saline or GDNF transplanted into the lesion gap. Four days post-injury, the rats were sacrificed. The GFP signal of dendrites in the T7-T9 cord was visualized via two-photon microscopy, then traced and analyzed. Our results indicated that the majority of FG labeled DPSNs in T7-T9 spinal cords were located in the Rexed Lamina VII, with greater than 90 percent glutamatergic neurons and the remaining 10 percent comprised of choline acetyltransferase, glycine, and GABA. Uninjured DPSNs had a predominantly dorsal-ventral distribution of dendrites. However, transection altered this dendritic distribution, with dorsal-ventral retraction and lateral-medial extension, and increased the density of spine-like structures. Transection caused cellular death closest to the lesion. Short-term GDNF treatment did not increase the number of surviving DPSNs but increased the terminal dendritic length and enhanced the transection effect on spine-like density. To our knowledge this is the first report describing the neurotransmitter expression and morphologic characteristics of DPSNs, as well as the dendritic response after transection injury and GDNF treatment.

Keywords: Descending propriospinal neuron, dendrite, spine, rabies virus, neurotransmitter, glial derived neurotrophic factor

T1-03

COMPUTATIONAL MODELING AND VALIDATION OF BRAIN DEFORMATION IN HUMAN VOLUNTEERS WITH RELEVANCE TO TRAUMATIC BRAIN INJURY

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Background: Knowledge of how brain deforms under physical forces is critical for understanding mechanics of TBI and for developing methods of prevention. The objective of this work is to compare deformation field obtained from the computer simulations with the experimental measurements of full-field deformation field in human brains.

Methods: To this end, we have developed subject-specific computational models of the human brain in human volunteers for which experimentally measured in vivo brain deformations are also available. For computational modeling of each subject, we incorporate information on brain morphology and white matter anisotropy from acquired T1-weighted and DTI scans, respectively. Computational simulations are performed using the Material Point Method (MPM). Loading conditions for the simulations are obtained directly from the experiments. The experiments involved sub-injurious rotational acceleration of the head about the inferior/superior axis with a peak angular accelerations of 200–250 rad/s^2. Dynamic deformation in each subject was measured using tagged MRI during the accelerations.

Results: The results of simulations are compared against the experimentally measured in vivo deformations (displacement and strain fields). Good agreement was seen between the simulations and the experiments in terms of predicted deformation patterns. Simulation results suggest that in these cases the brain deformation is dominated by shearing modes with peak shearing strains on the order of 4–6% in various substructures of the brain. It is also observed that global shearing of a brain tissue leads to local stretching in various substructures of the brain. Subject specific changes in morphology and anisotropy of brain tissue had an effect on the predicted local deformation pattern, although the global deformation pattern remained similar.

Conclusion: By combining state-of-the-art neuroimaging techniques with the computational mechanics based analysis, we elucidate mechanics of brain deformation in a living human brain.

Keywords: Brain Biomechanics, Computational Model, Tagged MRI, Validation

T1-04

ADOLESCENT BRAIN INJURY INDUCES CHRONIC MESOLIMBIC NEUROINFLAMMATION THAT COINCIDES WITH ENHANCED ADDICTION-LIKE BEHAVIOR IN MICE

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Substance use disorder is one of the most prevalent clinical psychiatric diagnoses among traumatic brain injury (TBI) patients. Recent epidemiological data suggests that 1) patients sustaining adolescent TBIs experience greater behavioral issues with substance abuse than control subjects, and 2) a history of TBI appears to be a possible risk factor contributing to the onset of cocaine use. Notably, virtually no data exists examining whether the preference for illicit drugs of abuse is affected by adolescent brain injury. Using the controlled cortical impact model of TBI coupled with the conditioned place preference (CCP) assay, we test the hypothesis that brain injury during adolescence exacerbates the reinforcing properties of cocaine in adulthood by affecting function of the reward pathway. Six-week old, male C57BL/6 mice sustained a single impact TBI of varying severity (mild or moderate) to the right somatosensory cortex. CPP pre-testing began 2 weeks post-TBI, followed by 6 days of intraperitoneal cocaine administration (10 mg/kg). The place preference shift was significantly enhanced in all treatment groups receiving cocaine compared to saline controls; furthermore, a moderate TBI during adolescence caused a significant increase in the place preference shift compared to non-surgical cocaine controls. Few reports have examined the presence and potential of mesolimbic neuropathology following brain injury. Using GFAP and IBA-1 immunofluorescence, we have observed persistent neuroinflammatory responses in the nucleus accumbens and ventral tegmental area following TBI. These results suggest that sustaining a moderate TBI during adolescence may augment addiction-like behavior in adulthood possibly related to mesolimbic neuroinflammation.

Keywords: Controlled Cortical Impact, Conditioned Place Preference, Cocaine, Mesolimbic Nuclei, Astrocyte, Microglia

T1-05

COGNITIVE DEFICITS DEVELOP 30D AFTER TBI AND ARE EXAGGERATED BY MICROGLIA-ASSOCIATED REACTIVITY TO PERIPHERAL IMMUNE CHALLENGE

Megan Muccigrosso[1], Joni Ford[1], Chris Burnsides[1], Ashley Fenn[1], Phillip Popovich[1], Jonathan Lifshitz[2], Rohan Walker[3], Daniel Eiferman[1], Jonathan Godbout[1]
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Traumatic brain injury (TBI) elicits immediate neuroinflammatory events that contribute to acute cognitive, motor, and behavioral disturbance. Despite resolution of these acute complications, cognitive impairment can develop after TBI. We have reported that a moderate midline fluid-percussion injury leads to a population of ''primed'' (MHCII+) microglia that develop and persist 1 month after injury. Moreover, these primed microglia are hyper-reactive to immune challenge and this is associated with amplified neuroinflammation and onset of depressive-like behavior. Therefore, the objective of this study was to determine the degree to which microglia priming and immune-reactivity causes cognitive impairment. Using the Barnes maze, a hippocampal-dependent learning-memory task, we show that a diffuse TBI interrupts retrograde memory acutely 7d after injury. Yet 7d after injury there were no acute deficits in anterograde learning. By 30d after TBI, however, significant anterograde learning impairments developed in TBI mice in the acquisition of the memory task. Moreover these cognitive deficits at 30d after TBI were exaggerated by peripheral immune challenge. For instance, 72h after LPS injection, TBI-LPS mice had more errors, increased time to find the escape, and spent less time in the escape quadrant during the probe trial. These deficits were not associated with alteration in the number

of new or doublecortin-positive neurons in the hippocampus. Morphological and mRNA evidence indicated a hyperactive profile of microglia in the TBI-LPS mice. For example, increased microglia (Iba-1+) in the CA3 of the hippocampus from TBI-LPS mice had an increased perimeter, max length, and proportional area. In addition, microglia from TBI-LPS mice had the highest levels of TNF and CCL2. Taken together, these data support the hypothesis that a diffuse TBI sensitizes the brain to secondary challenges that augment cognitive decline and impairment after injury.

Keywords: Microglia, Priming, Neuroinflammation, mFPI

T1-06

GENETIC AND PHARMACOLOGICAL MODULATION OF TRIGEMINAL PAIN MOLECULES IN A MODEL OF TRAUMATIC BRAIN INJURY

Brittany Daiutolo, Ashley Tyburski, Shannon Clark, Melanie Elliott
Thomas Jefferson University, Neurosurgery, Philadelphia, USA

Headache is the most common symptom of post-concussion syndrome, a highly prevalent disorder following mild to moderate traumatic brain injury (TBI). Headache may persist months to years beyond the expected period of healing from post-traumatic inflammation. A hypothesis that persistent inflammatory processes initiate and maintain the sensitization of trigeminal pain neurons promoting the development of chronic headache has been under investigation by our laboratory. Two key pain signaling molecules implicated in migraine, nitric oxide (NO) and calcitonin gene-related peptide (CGRP), may play a role in post-traumatic headache. Following TBI, release of nitric oxide (NO) is largely derived from the inducible nitric oxide synthase isoform (iNOS). CGRP is a well-studied nociceptive neuropeptide in migraine pathophysiology. The goal was to study the relationship of CGRP and iNOS in the trigeminal pain circuit in a model of a mild-moderate TBI, controlled cortical impact (CCI). Pharmacotherapies known to inhibit the actions of CGRP, a CGRP antagonist (MK8825) and sumatriptan, were administered post-injury and compared to saline controls. The effects of treatment on iNOS mRNA and protein were determined, as well as the cellular source and distribution of iNOS in the trigeminal ganglia and trigeminal nucleus caudalis (TNC). The effects of CCI in iNOS knockouts (KO) were compared to wild-type mice with CCI on CGRP levels in the TNC. Sensory behaviors indicative of headache were also measured. Allodynic thresholds were significantly increased in MK8825 and sumatriptan mice compared to CCI injured controls, $p < 0.01$. Photophobia was attenuated in MK8825 treated mice compared to vehicle treated mice, $p < 0.05$. Treatments significantly reduced the level of iNOS mRNA and immunoreactivity in the TNC and ganglia, $p < 0.01$. iNOS co-localized with neurons in the TNC and glial cells in the ganglia. Sumatriptan significantly reduced CGRP levels in the TNC, $p < 0.01$. iNOS deletion significantly attenuated CGRP at 3 days post-injury, $p < 0.05$. Findings support synergistic interactions between CGRP and iNOS following TBI and indicate a prolonged therapeutic window for CGRP-targeted treatment.

Keywords: CGRP, Nitric oxide

T1-07

LEVEL-SPECIFIC OPTIMIZATION OF CELLULAR INTERVENTION IN SPINAL CORD INJURY - A NEW PARADIGM

James Hong[1], Jian Wang[1], Yang Liu[1], Anna Badner[1], Rachel Dragas[1], Ahad Siddiqui[1], Stefania Forner[1], Reaz Vawda[1], Michael Fehlings[1,2]
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Although half of all spinal cord injuries (SCIs) occur at the cervical level (cSCI), thoracic SCI (tSCI) models are preferred due to reduced mortality. Recently, there has been a shift towards cSCI models given their higher clinical relevance. Despite differences in vascular supply, similar pathophysiological profiles between tSCI and cSCI have been assumed. Consequently, current cell therapy paradigms in cSCI are largely inefficacious. By elucidating the differences in the temporal profiles of secondary injury following cSCI and tSCI, modulations to the injury milieu followed by timed cellular intervention can then occur. We posit that temporal secondary injury profiles in SCI are level-dependent due to differences in vascular disruption and neuroinflammation post-SCI. Wistar rats received either a 23 g C6 or a 35 g T6 spinal cord clip-compression injury for 1-minute after laminectomy. At 3, 7, 14 days post-SCI, animals were sacrificed. Lesional and peri-lesional spinal cord tissue was processed for RNASeq and ELISA. An identical set of lesioned animals underwent high resolution ultrasound imaging for functional vascularity. Time-matched laminectomy rats were used as controls. Hierarchical clustering of RNASeq and ELISA arrays revealed that the majority of pro-inflammatory cytokine expression peaked at days 3 and 14 after cSCI, and at days 7 and 14 after tSCI. Most differentially expressed proteins were identified at days 7 and 14 between tSCI and cSCI, and enrichment analysis revealed these proteins to be involved in leukocyte differentiation and migration. This data correlates strongly with a significant improvement in functional vascularity from days 3–7 with a sharp decrease from days 7–14 after cSCI, while tSCI only decreased at day 7–14. For the first time, differences in pathophysiological profiles have been shown between tSCI and cSCI. Thus, level-specific paradigms for cellular intervention will be crucial for the successful clinical translation of cell therapy in SCI.

Keywords: injury niche, ultrasound and power doppler, high-throughput profiling, cervical spinal cord injury, thoracic spinal cord injury, neural precursor cells

T1-08

KETOGENIC DIET DECREASES OXIDATIVE STRESS AND IMPROVES MITOCHONDRIAL RESPIRATORY COMPLEX ACTIVITY

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Cerebral metabolism of ketones after traumatic brain injury (TBI) improves contusion volume and behavior in an age-dependent manner. Neuroprotection is attributed to improved cellular energetics, although other properties contribute to the beneficial effects. Oxidative stress is responsible for mitochondrial dysfunction after TBI. Ketones are reported to decrease oxidative stress, increase antioxidants and scavenge free-radicals. It is hypothesized that ketogenic diet (KD) will decrease post-TBI oxidative stress and improve mitochondria. Postnatal day 35 (PND35) male rats were given sham or controlled cortical impact (CCI) injury and placed on standard (STD) or KD. Ipsilateral cortex homogenates and mitochondria were assayed for markers of oxidative stress, antioxidant expression and mitochondrial function. Oxidative stress was significantly increased at 6 and 24 hrs post-injury and attenuated by KD while also inducing protein expression of antioxidants. Complex I activity was inhibited in both STD and KD groups at 6 hrs and normalized by 24 hrs. KD significantly improved Complex II-III activity that was

reduced in STD at 6 hrs. Activity continued to be reduced at 24 hrs in STD animals with no differences in KD animals. These results strongly suggest that ketones improve post-TBI cerebral metabolism by providing alternative substrates and through antioxidant properties, preventing oxidative stress mediated mitochondrial dysfunction.

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Keywords: traumatic brain injury, mitochondria, ketogenic diet, oxidative stress, juvenile

T1-09

EXPERIMENTAL DIFFUSE TRAUMATIC BRAIN INJURY INCREASES ASTROCYTE-SECRETED THROMBOSPONDIN-1 IN THE THALAMUS

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Publicity of neurological dysfunction induced after diffuse traumatic brain injury (dTBI) has highlighted the necessity to understand the causative pathophysiology. In rodents, dTBI leads to sensory sensitivity to whisker stimulation in the thalamocortical circuit, similar to light and sound hypersensitivity experienced by brain injury survivors. A proposed source of this morbidity is maladaptive circuit reorganization as a result of post-traumatic synaptogenesis. After neurological insult, the developmental synaptogenic protein thrombospondin-1 (TSP-1) would be primarily secreted by activated astrocytes in the adult CNS. We hypothesize a role for TSP-1 in mediating synaptogenesis after dTBI. For this study, adult male Sprague-Dawley rats underwent sham or moderate midline fluid percussion brain injury. At multiple time points post-injury, gene and protein expression of TSP-1 were quantified in thalamic biopsies using qPCR and automated capillary westerns. TSP-1 gene expression increased over time ($F(8,48 = 2.964; p = 0.0089$), with significance at 5 days post-injury (DPI) compared to uninjured shams. Similarly, TSP-1 protein expression increases over the first week post-injury ($F(5,16) = 3.972; p = 0.0156$), reaching significance at 7DPI in comparison to sham. Additionally, tissue sections were stained with glial fibrillary acidic protein (GFAP), a marker of activated astrocytes. Thalamic GFAP pixel density increased over time ($F(3,12) = 15.73; p = 0.0002$), with staining at 7 and 28DPI being greater than sham. This study identified a temporal profile for TSP-1 gene and protein expression after dTBI that coincides with evidence of activated astrocytes in the thalamus. TSP1-mediated synaptogenesis may play a pivotal role in thalamocortical circuit reorganization which subsequently leads to injury-induced neurological dysfunction. Understanding the temporal profile of synaptogenic events after dTBI may allow for mitigation of neurological dysfunction by pharmacologic and rehabilitative manipulation Partially supported by ADHS14-00003606, NIH-R03 NS-077098, NIH-R01 NS-065052, Science Foundation Arizona, PCH Mission Support.

Keywords: Thrombospondin, Traumatic Brian Injury, Thalamus, synapotogenesis

T1-10

PERIOPERATIVE HYPERTENSION PREDICTS WORSE FUNCTIONAL RECOVERY FOLLOWING THORACIC SPINAL CORD INJURY IN RATS

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Neurocritical care complications following spinal cord injury (SCI) may have long-lasting effects on neurological recovery. Although neurocritical care logs are maintained in animal research, they are rarely considered as relevant predictors of outcome. We curated 20 years of animal SCI research care logs to build a translational electronic medical record (trans-EMR) containing detailed data from physiology and bloodwork measures. To maximize utility of trans-EMR data for SCI decision-making, we applied topological data analysis (TDA), which deploys ensemble machine learning in multidimensional space to heterogeneous, complex big-data. Data queried from the VISION-SCI database ($N = 2719$) included adult male and female rats receiving graded thoracic bilateral SCI contusions (T9; MASCIS impactor; 12.5, 25 and 50 mm). Inclusion criteria: complete data for perioperative vitals (body temperature, heart rate, blood pressure), blood gases, weight monitoring, bladder care, locomotor function (1–6 weeks post-injury BBB scores) and terminal tissue sparing (6 weeks) ($N = 334$). TDA revealed a data-driven, syndromic relationship between perioperative care and locomotor recovery on a subset of the animals ($N = 72$). Cross-validation of TDA-identified patterns was performed on the remaining animals ($N = 262$) using an analytical workflow of TDA, a post-hoc repeated-measures general linear model (GLM) and bivariate correlations. TDA identified network dysfunction in BBB recovery, significantly predicted by hypertensive episodes ($MAP > 140$ mmHg) during SCI operation. Cross-validation in the independent data-set revealed a similar significant difference in BBB recovery inversely predicted by MAP. GLM on BBB recovery revealed MAP significantly predicted locomotion in both datasets, and correlational analyses confirmed an inverse relationship. Together the data indicate that perioperative hypertension predicts poor recovery following SCI, an effect size greater than the drug effects in multiple preclinical trials. Funding: Craig H. Neilsen Foundation 224308, NIH: NS067092, NS069537, NS079030, NS032000, NS088475, Wings for Life Foundation WFLUS008/12

Keywords: hypertension, spinal cord injury, topological data analysis, syndromics

T1-11

KINASES REGULATING GLUTAMATE TRANSPORTERS ARE DIFFERENTIALLY ACTIVATED AFTER LATERAL FLUID PERCUSSION

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Glutamate transporter expression and localization are potently regulated by protein kinases. We used a kinome array platform to determine global changes in serine-threonine kinase activity after lateral fluid percussion in prefrontal cortex (PHC) and hippocampus (HPC). In PFC 25 substrates had changes in phosphorylation status greater or less than 1.15 fold change from sham while in HPC 15 substrates exhibited a 1.15 fold change difference from sham. Using publically available algorithms and databases we mapped protein kinases predicted to target substrate sequences and performed random sampling permutation analyses to identify kinases targeting the reporter peptides at frequencies greater than what would be expected by chance. From kinases identified by the permutation analyses we constructed signaling network models based on known direct interactions in the Ingenuity database. We performed inhibitor studies in the prefrontal cortex using the kinome array platform to further investigate the role of several kinases implicated by our analyses and in the literature in TBI pathology. In pooled prefrontal cortical samples, we found differential regulation of protein kinase B (AKT) in the presence of the AKT inhibitor. In TBI samples, kinase activity increased on array substrates in the presence of AKT inhibitor, while kinase activity on substrates of the sham sample was decreased. Kinase activity in the presence of c-Jun kinase inhibitor or combine protein kinase C (PKC) and mitogen activated protein kinase kinase (MEK) showed much less divergence in activity profiles. Of the kinases identified in our analyses, AKT, PKC and protein kinase A (PKA) are known to actively regulate glutamate transporter expression, localization and transport activity and suggest dysfuntion in the balance of pro- and anti- glutamate reuptake mechanisms after brain injury.

Keywords: kinase, cell signaling, glutamate transport, AKT

T1-12

ADIPOSE STROMAL VASCULAR FRACTION CELL TREATMENT MITIGATES INCREASED CEREBROVASCULAR PERMEABILITY AFTER TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) is accompanied by a loss of memory that can be attributed to the formation of un-degradable complexes of proteins such as fibrinogen (Fg) and cellular prion protein (PrP^C). This complex can be formed as a result of increased cerebrovascular permeability resulting in deposition of Fg in the interstitium. We tested the hypothesis that adipose-derived stromal vascular fraction (SVF) cells, that are anti-inflammatory and reparative, can mitigate TBI-induced hyper-permeability and, by decreasing Fg-PrP^C complex formation, reduce memory loss. SVF cells collected from syngeneic mouse adipose tissue were intravenously injected into experimental mice the next day after TBI. Mice in control group were injected with vehicle alone. Ten days after TBI pial venular permeability was assessed by measuring the extravascular accumulation of fluorescently-labeled bovine serum albumin. Formation of Fg-PrP^C complexes in mouse brain vascular subendothelial matrix was assessed by immunohistochemistry. The novel object recognition test (NORT) was used to assess changes in short-term memory after TBI. Cerebrovascular protein leakage was reduced in mice infused with SVF cells ($131 \pm 3\%$) as compared to that in mice infused with vehicle alone ($186 \pm 6\%$) after TBI. Accumulation of Fg and PrP^C in the interstitium was mitigated by SVF cell treatment. NORT results showed that there was a tendency in reduction of memory loss in mice with SVF cells. These results suggest that TBI-induced cerebrovascular hyper-permeability to proteins can be ameliorated with SVF cells affecting vascular endothelium and leading to reduction of Fg-PrP^C complex formation and short-term memory loss. Thus, our data indicate a novel therapeutic role of SVF cells in treatment of vasculo-neuronal dysfunction after TBI.

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Keywords: Cerebrovascular permeability, Fibrinogen, Cellular prion protein, Endothelial repair, Short-term memory

T1-13

NEURONAL PLASMALEMMAL PERMEABILITY/DENDRITIC BEADING IN THE HIPPOCAMPUS FOLLOWING DIFFUSE BRAIN INJURY IN SWINE

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Closed-head traumatic brain injury (TBI) is generally caused by rapid angular acceleration/deceleration of the head, resulting in strain fields throughout the brain. However, the neuroanatomical distribution and loading thresholds of cells affected by these strain fields remain poorly understood. Our objective was to characterize the extent of immediate alterations in plasmalemmal permeability in the hippocampus following inertial TBI in swine. Swine underwent a closed-head rotational acceleration (single injury or two injuries separated by 15 minutes or 7 days). To assess plasmalemmal compromise, Lucifer Yellow (LY), a small (457 Da) cell impermeant dye, was administered into the lateral ventricles. Animals were sacrificed within 15 minutes (LY injections), 8 hours, or 7 days post-injury ($n = 29$ total). We found acute plasmalemmal permeability, predominantly neural cells. LY^+ cells were observed across different hippocampal regions, including the hilar region, dentate granule layer, and CA1 area. A decrease in NeuN immunoreactivity was observed in a subset of LY^+ cells, suggesting altered NeuN expression could indicate stressed neurons. In addition to LY in somata and neurites, morphological changes were observed via acute beading in dendritic fields projecting from dentate granule neurons. The effect was most pronounced following a single severe injury but also following repetitive mild injuries. Although mitochondrial dysfunction is a potential cause of beading, mitochondrial fission labeling did not co-localize with beading. Given the rapid onset of permeability and beading, these are likely acute biophysical disruptions due to diffuse strain fields. Ongoing analyses are assessing the neurophysiological, inflammatory, and degenerative changes associated with these structural responses. Understanding trauma-induced biophysical responses and pathophysiological progression is necessary to guide development of therapeutics to ameliorate afflicted cell populations following inertial TBI.

Keywords: traumatic brain injury, biomechanics, plasma membrane, cell permeability

T1-14

COMT AND ANKK1 GENETICS INTERACT WITH DEPRESSION TO INFLUENCE BEHAVIOR FOLLOWING MODERATE/SEVERE TBI

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Polymorphisms in the dopamine system, specifically the functional polymorphism Val158Met in the catechol-o-methyl transferase (COMT) gene and the Taq1A polymorphism in the ankyrin repeat and kinase domain containing 1 (ANKK1) gene, are associated with problematic behavior (e.g. impulsivity, aggression) in healthy populations. Additionally, stressful environments can interact with DA genetics to influence behavior. To determine whether depression, a condition associated with stress, interacts with polymorphisms to adversely influence behavior following TBI, we assessed behavior and depression status with the Frontal Systems Behavioral Scale (FrSBe) and the Patient Health Questionnaire (PHQ-9) at 6&12 months in a population of 97 Caucasian individuals with TBI. The FrSBe assesses behaviors associated with frontal lobe dysfunction and produces t-scores based on age, sex, and education adjusted norms. The PHQ9 is a validated assessment in the TBI population for depression. At 12-months post-injury, we found a significant interaction between depression and both Taq1A ($p=0.003$) and Val158Met ($p=0.030$) polymorphisms with regard to FrSBe scores. Depressed A2-homozygotes scored $\sim$20 points worse than depressed A1-carrier counterparts ($p=0.053$), and depressed Met-homozygotes scored $\sim$23 points worse than depressed Val-carriers ($p=0.064$). Those without depression did not differ in behavior by Taq1A status ($p=0.651$) or Val158Met status ($p=0.464$). A significant gene*depression interaction ($p=0.002$) was also found at 12-months when assessing concurrent effects of Taq1A and Val158Met status on behavior. Depressed individuals who were A2/A2 and Met-homozygotes reported worse behavior than A2/A2 OR Met -homozygotes ($p=0.003$) and those with no risk alleles ($p=0.023$). Significant interactions were also noted on Apathy ($p=0.006$), Executive Function ($p=0.002$), and Disinhibition ($p=0.045$) subscales. Similar, but non-significant, trends were observed at 6-months. DA genetics may inform biosusceptibility to behavioral problems following TBI and may help identify ''at-risk'' individuals with the greatest need for behavioral intervention.

Keywords: Rehabilomics, genes, behavior

T1-15

DELAYED AND ABBREVIATED ENVIRONMENTAL ENRICHMENT AFTER EXPERIMENTAL TRAUMATIC BRAIN INJURY INCREASES HIPPOCAMPAL NEUROGENESIS

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Continuous environmental enrichment (EE) exposure improves neurobehavioral outcome after experimental traumatic brain injury (TBI). One likely mechanism for the benefit is increased neurogenesis. Delayed and abbreviated EE, which is more akin to clinical rehabilitation in terms of timing, also enhances neurobehavioral recovery comparably to early and continuous exposure after TBI; however, its effect on hippocampal neurogenesis is unknown. Therefore, *the aim of this study was to test the hypothesis that delayed and abbreviated EE is sufficiently robust to induce hippocampal neuroplasticity after TBI*. Anesthetized adult male rats received a controlled cortical impact (2.8 mm depth at 4 m/sec) and were randomly assigned to either standard housing (TBI + STD), continuous EE (TBI + EE), or delayed and abbreviated EE (TBI + EE, 3 day delay, 6 hr day). BrdU (500 mg/kg) was provided twice per day for 3 days and then sacrificed 10 days later. The brains were cut on a freezing microtome at 40 μm and immunostaining for BrdU or triple immunofluorescence for BrdU, DCX and NeuN was performed. Continuous EE lead to a 91% ($p \leq 0.05$) increase in BrdU labeled nuclei density in the subgranular zone of the dentate gyrus when compared to STD. Abbreviated EE resulted in a 156% increase ($p \leq 0.01$) relative to STD. Triple immunofluorescence showed there were no differences in the percentage of BrdU/DCX or BrdU/NeuN double labeled cells among the groups; however in the continuous EE group, DCX positive cells displayed larger ramifications when compared to abbreviated EE. In conclusion, abbreviated EE with a 3 day delay effectively induced hippocampal neurogenesis after TBI, which supports the hypothesis. These findings elucidate a possible mechanism for the benefits observed with both continuous and delayed-and-abbreviated EE.

Keywords: controlled cortical impact, environmental enrichment, neurogenesis, immunostaining

T1-16

DEPRESSIVE SYMPTOMS ALTER AMYGDALA CONNECTIVITY IN TRAUMATIC BRAIN INJURY

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Depression is one of the most common psychiatric conditions in chronic Traumatic Brain Injury (TBI). While depression has detrimental effects on chronic TBI individuals, there have been few investigations of neuroimaging biomarkers for comorbid depression in TBI. Here, we utilized resting-state functional Magnetic Resonance Imaging to identify altered amygdala connectivity in individuals with chronic TBI who exhibited comorbid depressive symptoms ($N=30$), relative to chronic TBI individuals having minimal depressive symptoms ($N=24$). Connectivity analysis of these TBI sub-groups revealed that the TBI + depressive symptoms group showed relatively increased left amygdala connectivity with the bilateral precuneus, dorsal and medial superior frontal gyri and paracentral lobules; the left postcentral gyrus; the right insula, lingual gyrus, anterior prefrontal gyrus and precentral gyrus ($p_{cluster} < 0.05$, $p_{voxel} < 0.005$). The TBI + depressive symptoms group also exhibited relatively increased right amygdala connectivity with the bilateral middle cingulate cortices, insulae, dorsal and medial superior frontal gyri, paracentral lobules, pre- and postcentral gyri, dorsolateral prefrontal gyri and lingual gyri; left inferior frontal gyrus, dorsal anterior cingulate cortex, anterior fusiform gyrus and anterior cerebellar vermis; right thalamus and caudate head as well as relatively reduced right amygdala connectivity with the left caudate body and the right caudate tail. We conducted a post-hoc analysis on selected regions of interest analysis that showed group differences in amygdala connectivity

($p_{cluster} < 0.005$, $p_{voxel} < 0.005$). This resulted in spatially distinct correlation patterns of amygdala connectivity with the Buckley cognitive, affective and somatic factors of the Beck Depression Inventory-II. These results indicate that amygdala connectivity may be a potentially effective neuroimaging biomarker for comorbid depressive symptoms among chronic TBI individuals.

Keywords: Amgydala, fMRI, Resting-state, functional connectivity, Depression, TBI

T1-17

SLOWED CALLOSAL FUNCTION IN TBI LINKED TO IMPAIRED WHITE MATTER INTEGRITY

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The corpus callosum is the most widely reported area of disruption in traumatic brain injury (TBI). Here we present data linking disrupted corpus callosum (CC) integrity to slowed callosal function in pediatric moderate/severe TBI in the post-acute phase (1–6 months post injury). We examined 63 participants: 32 TBI (mean age = 14.2, 9 female), and 31 controls (mean age = 14.9, 14 female). We used visual ERPs (event related potentials) to measure IHTT (interhemispheric transfer time, msec). EEG was recorded during a visual pattern matching task. To assess white matter integrity, we used a method developed in our lab, autoMATE (automated multi-atlas tract extraction), to generate along-tract measures of fiber integrity. The distribution of IHTTs showed a bimodal distribution within the TBI group: some had IHTTs within 1.5 SD from the control mean, but others differed significantly (group cut-off = 18 msec min). We ran an element-wise linear regression testing for differences in FA and MD between the IHTT-slow TBI group and controls, and the IHTT-normal TBI group and controls. IHTT-slow and control groups differed significantly: the IHTT-slow group had lower FA and higher MD across large areas of the CC and beyond. There were minimal differences in FA between the IHTT-normal and control groups, and none in MD. Our results indicate that TBI can cause damage to myelin integrity, impairing the function of those tracts.

Keywords: IHTT, ERP, DTI, pediatric, traumatic brain injury, corpus callosum

T1-18

INTRANASAL INSULIN TREATMENT OF TRAUMATIC BRAIN INJURY: EFFECTS ON MEMORY AND CEREBRAL METABOLISM

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Traumatic brain injury (TBI) is often followed by a period of cerebral hypometabolism. Impaired cerebral glucose uptake directly affects long term patient outcome and is associated with cognitive and physical deficits. Intranasal insulin, which bypasses the blood brain barrier (BBB) to directly treat the brain, increases cerebral glucose uptake in Alzheimer's disease patients, and significantly improves memory function in these patients. Our preliminary data has demonstrated that 7 days of intranasal insulin treatment increased speed of completion of a beam walk task in a rodent model of TBI and increased viability of neurons and the number of anti-inflammatory microglia in the hippocampus. We therefore hypothesized that intranasal insulin would rescue cerebral metabolic function and cognitive deficit resulting from TBI in a chronic treatment model.

Adult male Sprague Dawley rats were exposed to a moderate controlled cortical impact (CCI) injury followed by intranasal insulin or saline treatment beginning 4 hours post-injury and continuing with daily administration for 14 days. Positron emission tomography (PET) scanning of radioactively labeled glucose (FDG^{18}) was performed prior to injury and again at 48 hours and 10 days post-injury. A significant depression in glucose uptake was observed in both insulin and saline treated groups, but a trend towards returning to baseline values was observed in the ipsilateral hippocampus and hypothalamus of the insulin treated group at 10 days post injury. Cognitive testing with the Morris water maze revealed that intranasal insulin significantly increased memory function in comparison to saline treatment, as measured by probe trial island crosses. An analysis of the search strategy used during the probe trial revealed that the insulin treated animals performed significantly better than saline treated animals. Tissue was also collected for assessment of macrophage and astrocyte activity and neuronal viability.

Overall, we now show that intranasal insulin increases memory function and has the potential to increase cerebral glucose uptake after TBI. These data support our hypothesis that intranasal insulin, a drug approved for clinical trials for the treatment of Alzheimer's disease, is effective in improving outcome following TBI.

Keywords: memory, insulin, PET, FDG18

T1-19

THE ROLE OF THE ATP-SENSITIVE POTASSIUM CHANNEL IN THE VASCULAR DYSFUNCTION ASSOCIATED WITH REPETITIVE MILD TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) has been associated with impaired ATP-sensitive potassium (K_{ATP}) channel function in both the neuronal and vascular compartments. Both L-arginine and L-lysine are required to activate the K_{ATP} channel and exert both neuronal and vascular protection. While these protective effects have been confirmed following uncomplicated TBI, their potential beneficial effects following repetitive TBI have not been established. In this study, we investigated

the role of the K_{ATP} channel in vascular dysfunction targeted by either L-arginine or L-lysine following repetitive mild TBI.

Adult male Sprague Dawley rats were subjected to repetitive mild TBI using impact-acceleration injury. Pial vascular function was assessed through the use of cranial windows. Pial arteriolar K_{ATP} channel function was assessed following repetitive mild TBI by measuring vascular reactivity to topical application of pinacidil, a K_{ATP} channel opener. We then evaluated the protective effects of intravenous administration of L-arginine and L-lysine on repetitive mild TBI by measuring vascular reactivity following the topical application of Acetylcholine.

Following repetitive mild TBI, the pial arterioles failed to dilate to pinacidil implicating the K_{ATP} Channel. Acetylcholine induced vascular reactivity was also impaired after repetitive mild TBI; however, protection occurred with L-arginine (5 mg/kg) administration, with the best results achieved when L-arginine was administered prior to the second/repetitive injury. Comparable cerebrovascular protection was not achieved with the same concentration of L-lysine; however, higher doses of L-lysine (20 mg/kg) proved protective.

Collectively, these studies demonstrate that repetitive mild TBI impairs cerebrovascular reactivity via K_{ATP} channel dysfunction. Additionally, this impaired vasoreactivity could be maximally preserved with the early use of L-arginine administration, suggesting its potential therapeutic utility. The enhanced benefits achieved with low dose L-arginine in comparison to L-lysine, may be explained by the fact that L-arginine also acts as precursor of nitric oxide in addition to its K_{ATP} channel function.

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Keywords: ATP-sensitive potassium channel, L-arginine, L-lysine, repetitive mild traumatic brain injury, vascular reactivity

T1-20

ADVANCED DIFFUSION MRI-BASED RADIOLOGICAL-PATHOLOGICAL CORRELATIONS IN CHRONIC TRAUMATIC ENCEPHALOPATHY

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Chronic traumatic encephalopathy (CTE) is a progressive degenerative disorder associated with repetitive traumatic brain injury (TBI). Post-mortem studies report hyperphosphorylated tau pathology in CTE, most notably in perivascular, periventricular and sulcal depth grey matter as well as axonal injury. Currently a diagnosis of CTE is restricted to post-mortem neuropathological analysis. However, advanced neuroimaging methods, such as diffusion MRI, may provide the necessary microstructural information to differentiate CTE related pathology. We are in the process of testing this hypothesis using diffusion MRI acquired from *ex vivo* brain samples to determine the sensitivity and specificity of the radiological-pathological relationship in CTE.

Cortical and hippocampal samples of 2 CTE pathology, 2 non-CTE pathology, and 2 control formalin fixed post-mortem brains were obtained from BU CTE Center brain bank. Diffusion MRI data was acquired using the 11.74 T MRI scanner at Washington University. MRI sequence acquisition was optimized to produce high spatial resolution data with $250 \times 250\ \mu$m voxel dimensions in $500\ \mu$m slices and calculation of traditional diffusion tensor and non-tensor based methods, including diffusion kurtosis imaging (DKI) and generalized q-space imaging (GQI) parameters. Following MRI acquisition tissue blocks were serially sectioned at $50\ \mu$m thickness and tested for phosphorylated tau immunoreactivity using AT8 monoclonal antibody. Mounted tissue sections were co-registered with diffusion MRI data to quantify the relationship between diffusion parameters and positive tau staining. Initial analyses show that diffusion MRI parameters significantly differ between regions of dense tauopathy compared to normal cortical tissue. Differences in diffusion MRI parameters, indicative of microstructural abnormalities were also detected in white matter adjacent to cortical tau pathology.

The results of this study indicate that advanced diffusion MRI has the potential to detect microstructural alterations related to hyperphosphorylated tau pathology and adjacent axonal abnormalities seen in CTE. The long-term goal is to advance future non-invasive methods of accurately diagnosing CTE during life.

Keywords: Chronic Traumatic Encephalopathy, diffusion MRI, Tau Pathology, Radiological-Pathological Correlation

Open Communications

S10 Open Communication: TBI

S10-01

PREVENTING POSTTRAUMATIC EPILEPTOGENESIS BY STIMULATING CORTICAL EXCITATORY ACTIVITY AFTER TRAUMATIC BRAIN INJURY

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Homeostatic synaptic plasticity has been proposed to underlie acquired epileptogenesis. This hypothesis suggests that loss of neuronal activity following brain injury will initiate epileptogenesis while stimulating neuronal activity may prevent it. However, whether stimulating neuronal activity can prevent posttraumatic epileptogenesis has not been directly tested. In the partially isolated neocortex model of posttraumatic epileptogenesis (undercut) in mice, we made patch clamp recording from cortical layer V pyramidal neurons and found that spontaneous action potential firings in these neurons were significantly reduced at both 1 and 7 days after injury. The frequencies of both spontaneous excitatory and inhibitory synaptic currents (sEPSCs and sIPSCs) were also significantly depressed but without significant changes in the amplitudes of these events. In Thy1-channelrhodopsin-2 (ChR2) transgenic mice that express ChR2 in cortical layer V pyramidal neurons, we made undercut injury and applied optogenetic stimulation of the injured cortex using LED light for 7 days *in vivo*. Chronic optogenetic stimulation resulted in increased seizure threshold as indicated by a higher drug dosage required for inducing seizure and a longer latency period in pentylenetetrazol (PTZ) test, and reduced cortical hyperexcitability as indicated by decreases in the percentages of slices and mice in which epileptiform activity could be evoked in field potential recording. The frequencies of both sEPSCs and sIPSCs in neurons after optogenetic stimulation were significantly lower that the control undercut mice. The results support that homeostatic plasticity plays a role in the posttraumatic epileptogenesis and that stimulating activity of cortical excitatory neurons has prophylactic effect on posttraumatic epileptogenesis.

Keywords: Homeostatic plasticity, Optogenetic, Posttraumatic epileptogenesis, Cerebral cortex

S10-02

CHRONIC NEUROPHYSIOLOGICAL RECORDING OF THE HIPPOCAMPUS IN AWAKE BEHAVING SWINE AFTER DIFFUSE BRAIN INJURY

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We have previously established an acute recording methodology to interrogate hippocampal circuitry after diffuse brain injury (DBI) in a swine model of rotational injury. Injuries were administered over a range of coronal rotational accelerations (180260 rad/sec) that induced little or no loss of consciousness (<15 min), yet exhibited axonal pathology. Limitations of electrophysiological recording under anesthesia have led us to develop a chronic hippocampal electrode implantation model in the awake, freely moving swine, allowing examination of hippocampal networks engaged in relevant behavior after injury. Repeated concurrent electrophysiological and behavioral measures enable examination of how network level interactions may be disrupted after DBI. We have developed a stereotaxic surgical technique for precise implantation of a custom 32-channel silicone electrode into the swine hippocampus that allows for recordings of both single units in layer CA1 and dentate, as well as simultaneous laminar field potentials while the animal is awake and freely moving during behavioral tasks. We have also developed a novel object recognition task for swine, a behavior known to be hippocampal dependent. Pigs were trained on this task prior to electrode implantation. Preliminary behavioral results indicate that sham injured swine reliably interact longer with novel objects versus familiar objects. Moreover, we demonstrate robust extracellular field potentials out to 5 months post-implantation, as well as stable unit recordings pre- and post-implantation. Using spectral density analysis we report a prominent peak in hippocampal theta rhythm power in the freely behaving pig with positive shifts in peak frequency and peak power during periods of locomotion. This dominant hippocampal rhythm has previously been shown to be disrupted in rodent traumatic brain injury models. Here we demonstrate the feasibility of combining chronic hippocampal electrophysiological recordings with concurrent behavior in freely moving large animals. Combining this methodology with our established DBI model in pigs may reveal mechanisms of trauma-induced network dysfunction which may lead to innovative neuromodulatory therapies.

Keywords: electrophysiology, behavior, rotational injury, mild TBI

S10-03

ABBREVIATED ENVIRONMENTAL ENRICHMENT CONFERS ROBUST NEUROBEHAVIORAL AND COGNITIVE BENEFITS IN BRAIN INJURED FEMALE RATS

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To establish an efficacious therapy for traumatic brain injury (TBI) a variety of relatively invasive strategies have been evaluated. Environmental enrichment (EE) is a non-invasive paradigm that promotes significant cognitive recovery after experimental TBI and has the potential to mimic post-TBI neurorehabilitation. However, the typical EE paradigm consists of continuous exposure, which is inconsistent with the clinic where physiotherapy is typically limited (Matter et al., 2011). Moreover, females make up approximately 40% of the clinical TBI population, yet they are rarely studied in TBI research. Hence, the goal of this study was to *test the hypothesis that abbreviated EE would confer neurobehavioral and cognitive benefits in brain injured female rats.* Anesthetized female rats received a controlled cortical impact (2.8 mm tissue deformation at 4 m/s) or sham injury (i.e., no impact) and were randomly assigned to TBI + EE (4 hr), TBI + EE (6 hr), TBI + EE (continuous), or TBI + STD groups, and respective sham controls. Motor function (beam-balance/beam-walk and rotarod) was assessed on post-operative days 1–5 and every other day from 1–19, respectively. Spatial learning/memory (Morris water maze) was evaluated on days 14–19. The data showed that EE, regardless of dose, improved motor function compared to STD housing ($p < 0.0001$). However, only continuous and 6-hr EE enhanced cognitive function ($p < 0.0001$). These data demonstrate that abbreviated EE confers robust neurobehavioral and cognitive benefits in TBI female rats, which supports the hypothesis and strengthens the validity of EE as a pre-clinical model of neurorehabilitation. Ongoing studies from our laboratory are evaluating further the benefits of abbreviated EE by combining it with pharmacotherapies, which may result in additive or synergistic benefits, thus facilitating recovery after TBI.

Keywords: Brain Injury, Controlled Cortical Impact (CCI), Environmental Enrichment, Females

S10-04

NEUROINFLAMMATORY MYELOID CELL PROCESSES ASSOCIATE WITH DIFFUSELY INJURED AXONS FOLLOWING MILD TRAUMATIC BRAIN INJURY IN MICROPIGS

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Mild traumatic brain injury (MTBI) is a prevalent disease that exacts significant personal and societal cost. The pathophysiology of MTBI is complex, with reports of diffuse axonal injury (DAI) being highly correlated to prolonged morbidity. Progressive chronic neuroinflammation has also recently been correlated to morbidity, however, the potential association between neuroinflammatory myeloid cells and DAI is not well understood. The majority of studies exploring neuroinflammatory responses to TBI have focused on more chronic phases of injury and phagocytosis associated with Wallerian change. Little, however, is known regarding the neuroinflammatory responses seen acutely following diffuse MTBI and potential relationships to early DAI, an issue that has significant clinical relevance. Additionally, inflammation has recently been shown to be drastically different in rodents as compared to gyrencephalic humans. Accordingly, we employed a modified central fluid percussion model of MTBI in gyrencephalic micropigs and assessed potential associations between acute DAI and neuroinflammation within 6h of injury. This model generated substantial DAI in the thalamus (10.31 ± 1.34 APP+ swellings/0.72 mm^2 field), an area commonly affected across the spectrum of TBI. Extensive neuroinflammation was also observed following MTBI in the same thalamic sectors. Importantly, physical contact between Iba-1+ myeloid cell processes and the APP+ swellings of axons sustaining DAI was nearly double (0.16 ± 0.02 contacts/mm) compared to uninjured myelinated axons in sham animals (0.09 ± 0.01 contacts/mm). While active phagocytosis was observed in association with Wallerian degeneration, the Iba-1+ cells that contacted DAI swellings did not reveal ultrastructural changes consistent with phagocytosis. This is the first study to show direct physical correlation between the acute phase proximal axonal swellings and non-phagocytic neuroinflammation in a higher order animal. These findings could lead to a more complete understanding of acute neuroinflammation following MTBI and its potential as a diagnostic and/or a therapeutic target. This work was performed as a component of the Operation Brain Trauma Therapy consortium, which is supported by DoD grant W81XWH-10-1-0623.

Keywords: Neuroinflammation, Diffuse axonal injury, Micropig, Central fluid percussion injury, Quantitative image analysis

S10-05

CHARACTERIZATION OF ENDOGENOUS BRAIN-DERIVED NEUROTROPHIC FACTOR EXPRESSION IN RESPONSE TO PENETRATING BALLISTIC-LIKE INJURY

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Brain-derived neurotrophic factor (BDNF) has been shown to play a key role in mediating neurogenesis and synaptic plasticity in the adult central nervous system. However, little is known about the changes in this endogenous molecule following penetrating ballistic-like injury (PBBI). The aim of this study was to identify the regional and temporal alterations in BDNF levels in relationship to downstream neuroplasticity markers in the PBBI model. Adult male Sprague-Dawley rats received either sham (craniotomy only) or PBBI (10% injury severity) surgery, and were euthanized at 24h, 48h, 72h, and 7 days post-injury for BDNF quantification, and at 7, 14 and 28d post-injury for neuroplasticity assessments (n = 5–6/time-point). BDNF levels were quantified in hippocampus and cerebral cortex by ELISA assay, and growth-associated protein-43 (GAP-43) and synaptophysin (SYN) immunohistochemistry was performed to assess axonal and synaptic plasticity, respectively. Following immunostaining, the integrated density in the hippocampal region was determined using NIH Image J software. Results showed significant reductions in BDNF levels that were detected bilaterally in cortical and hippocampal regions at 7 days post-injury ($p < 0.05$ vs. sham), but not at the earlier time points. PBBI significantly decreased GAP-43 expression in the ipsilateral hippocampus at 14d and 28d post-injury, and in the contralateral hippocampus at 14d post-injury ($p < 0.05$ vs. sham). Similarly, significant reductions in SYN staining were detected at 14d and 28d post-injury in the ipsilateral hippocampus and at 14d post-injury in the contralateral hippocampus ($p < 0.05$ vs. sham). Collectively, these findings demonstrate that PBBI results in a delayed down-regulation of BDNF levels that precede subsequent reductions in neuroplasticity markers. These results suggest a critical role of BDNF in modulating endogenous neuroplastic response to brain injuries, underscoring the potential importance of supplementing growth factors to enhance neuroplasticity for promoting functional recovery after PBBI.

Keywords: BDNF, Synaptophysin, GAP-43, PBBI

S11 Open Communication: SCI

S11-01

THE CGRP8-37 RECOMBINANT PEPTIDE CONSTRUCT TO REDUCE CHRONIC PAIN FROM RAT SPINAL CORD INJURY

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Chronic pain following spinal cord injury (SCI) is challenging clinical problem with few effective treatments. It is necessary to identify new therapeutic targets and approaches. Calcitonin gene related peptide (CGRP) is produced by neurons in the dorsal root ganglia and thought to play a key role in nociceptive neurotransmission in the spinal dorsal horn. Hypersensitivity to CGRP and/or sprouting in response to injury may contribute to allodynia and hyperalgesia in persistent neuropathic pain. A truncated CGRP peptide, $CGRP_{8-37}$, can reverse symptoms of neuropathic and inflammatory pain in animal models. This study aims to test the analgesic potential of the neuropathic pain gene therapy candidate $CGRP_{8-37}$. The $CGRP_{8-37}$ fragment from human CGRP cDNA was cloned to the peptidylglycine-amidating monooxygenase (ssPAM/pGEMT) signal peptide to allow $CGRP_{8-37}$ to be amidated and secreted, and subcloned into AAV- and Lenti-EGFP plasmids. Immunocytochemical colocalization of anti-CGRP and Golgi marker anti-Giantin antibody confirmed secretable $CGRP_{8-37}$ peptide. For initial screening, $CGRP_{8-37}$ supernatant transfected HEK cells was intrathecally injected into rats with chronic constriction injury (CCI) and formalin-evoked inflammatory pain model. Results showed that reduction of mechanical, tactile, cold allodynia and formalin-evoked pain responses treated with AAV-$CGRP_{8-37}$ supernatant was comparable with the effect of 10 nM $CGRP_{8-37}$ peptide, but not in controls. Spinal cord clip compression injury was induced pain-related behavior in rats. At 4 weeks post-injury when pain-related behavior was clearly established, animals were injected with lenti-ssPAM-$CGRP_{8-37}$-EGFP or control virus intraspinally into lumbar dorsal horn. Attenuation of tactile, mechanical and cold allodynia was observed by 2 weeks post injection with gradual improvement of behavioral outcomes towards pre-injury levels by 12 weeks post-SCI. In contrast, allodynia persisted in rats receiving control virus. Our findings suggest that engineered analgesic $CGRP_{8-37}$peptide have the potential to alleviate SCI-induced pain.

Supported by the Sheila and David Fuente Neuropathic Pain Program, University of Miami Research Support Award, and Buoniconti Fund to Cure Paralysis

Keywords: CGRP8-37, spinal cord injury, gene therapy, chronic pain

S11-02

LONGITUDINAL OPTOGENETIC MAPPING OF THE CORTICOSPINAL TRACT AS A NOVEL APPROACH FOR FUNCTIONAL EVALUATION OF SPINAL CORD INJURY

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Spinal cord injury (SCI) causes immediate disruption of ascending and descending pathways, which are commonly followed by plasticity and reorganization of these pathways at various levels of the central nervous system. For the motor system, evaluating longitudinal changes in the integrity and function of the corticospinal tract (CST) following SCI is important for understanding injury mechanisms and assessing the efficacy of therapeutic interventions. However, no techniques are currently available for this purpose. Our goal was to use *in vivo* transcranial optogenetic mapping of the motor cortex for longitudinally assessing the function of the CST after SCI. In transgenic mice that expressed channelrhodopsin-2 in cortical layer V pyramidal neurons, we used a blue laser to scan the region of motor cortex through intact skull. Optogenetically evoked limb movements were precisely detected by motion detectors or by recording electromyogram (EMG). In uninjured mice, motor maps of the forelimb area made at different times were generally stable and reproducible. To determine whether optogenetic mapping would reflect CST function at different stages after SCI, we simultaneously assessed changes in motor maps and motor behavior of the forelimb before and at different times following unilateral pyramidotomy or cervical spinal hemicontusion. Unilateral pyramidotomy caused immediate loss of the forelimb motor area, which was followed by partial recovery of motor map and behavior in 3–4 weeks after SCI. In contrast, spinal hemicontusion at the cervical level (C5) resulted in an acute expansion of the motor map, which was followed by progressive loss of map area and impairment of motor behavior at 3–4 weeks after injury. Further analyses indicated positive correlations between map size and motor function. We conclude that optogenetic mapping of cortical motor area may be an efficient and minimally invasive technique for longitudinal functional evaluation of the CST following SCI.

Keywords: Optogenetic, Motor cortex, Spinal cord injury, Corticospinal tract

S11-03

3D IMAGING OF AXONS IN TRANSPARENT SPINAL CORDS FROM RODENTS AND NON-HUMAN PRIMATES

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Failure of axons to regenerate is the primary reason for paralysis after spinal cord injury (SCI). Thus, discovering mechanisms to promote axon regeneration has been an intense area of research. A technical challenge has been visualizing axon trajectory in the injured spinal cord to provide clear origin-target information. Recent advances in tissue clearing methods have made it possible to overcome this hurdle, but previous studies have been performed with transgenic mice in which the axons were pre-labeled with green fluorescent protein (GFP). Thus, while these studies have provided a proof-of-concept, a more practical approach to investigating axon regeneration requires axon tracing. Using mouse and rat models of SCI, we labeled different axon tracts using several types of adeno-associated viruses and performed tissue clearing to image axons using light sheet (LSFM) and confocal microscopy. AAV8-pUBC-eGFP and tdTomato viral axon labeling combined with a tetrahydrofuran (THF)/benzyl alcohol-benzyl benzoate (BABB) tissue clearing method is effective in visualizing different axons in the intact and injured mouse and rat spinal cord. While a LSFM can image the spinal cord with exceptional speed, fine axonal projections such as corticospinal axons are better suited for confocal microscopy imaging.

Keywords: Clearing, LSFM, Spinal cord injury, Light sheet fluorescence microscopy, 3Disco, CST and RST

S11-04

TARGETING THE TRPV4 CHANNEL TO REDUCE INFLAMMATION AND IMPROVE OUTCOME FOLLOWING SCI

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Trauma to the spinal cord elicits a profound inflammatory response both within the damaged cord as well as throughout the rest of the body. This inflammatory response is further characterized by the activation and mobilization of systemic as well as CNS immune components that are thought to provide both beneficial as well as pathological aspects to the healing process. Mechanisms underlying the activation and progression of this immune/inflammatory activation continue to be unveiled. The Transient Receptor Potential channel, subfamily V, member 4 (TRPV4) is a calcium-permeable, nonselective cation channel expressed throughout the body and serves as a molecular and mechanical sensor to detect alterations in temperature, osmolality blood pressure, etc. Due to TRPV4's association with endothelial cells and role as regulator of vascular tone, we hypothesized that aberrant activation of TRPV4 via mechanical insult may worsen spinal vascular leakage produced by contusion injury. We determined that blood-spinal cord-barrier (BSCB) breakdown was reduced in TRPV4-null mice compared to wild type (WT) when assessed 48 hours post-spinal contusion injury. Utilizing additional mutant mice in which TRPV4 is linked to GFP, we observed strong co-association of GFP with both spinal microglia as well as splenic macrophages. This lead us to hypothesize that TRPV4 activation following spinal cord injury (SCI) may contribute to systemic immune activation/inflammation following SCI. WT mice were treated with the selective TRPV4 inhibitor, HC-067047, once daily (10 mg/kg) for three days. We observed that HC-067047 treatment lead to a significant reduction in both microglial and astrocytic activation at the lesion site compared to vehicle-treated controls. In addition, HC-067047-treatment significantly attenuated the loss in splenic mass normally observed following CNS trauma. Our results suggest that trpV4 inhibition may attenuate both spinal and systemic immune activation/inflammation following SCI.

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Keywords: blood spinal cord barrier, spleen, neuroimmune, trpv4, macrophages

S11-05

ATTENUATING GASTROINTESTINAL VASCULAR PERMEABILITY AFTER SPINAL CORD INJURY

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Gastrointestinal (GI) hemorrhage is a dangerous complication after spinal cord injury (SCI). Undiagnosed abdominal complications are the third leading cause of death in paraplegic and quadriplegic patients after the acute phase of injury. The main objectives of this study is to investigate the compromise of the GI vascular permeability in mice during the acute phase of injury and to determine if this compromise can be attenuated by an intravenous (IV) administration of angiopoietin-1 (Ang-1). Ang-1 is a vascular stabilizing protein expressed constitutively by endothelial cells, pericytes, astrocytes, smooth muscle cells, and fibroblasts. The study examined GI vasculature permeability using dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) 48 hours after a spinal contusion injury. The contusion injury was delivered using the Infinite Horizon Impactor (60 kDynes with a 1 second dwell time) at thoracic level 8. Treatments groups received a single IV administration of Ang-1 (30 μg, 100 μg, or 300 μg) through the jugular vein three hours following injury. Controls groups received an IV administration of saline. DCE-MRI analysis indicated that there is a significant increase in GI vascular permeability in injured animals compared to uninjured animals at 48 hours after injury. We observed a significant decrease in GI vascular permeability following a single IV injection of Ang-1 (300 μg) compared to saline treated animals. In addition, Ang-1 treatment produced a qualitative improvement in GI morphological outcome. SCI produced disruption in GI villi compared to naive, uninjured control mice in H&E stained GI tract sections. Ang-1 (300 μg) treated animals exhibited reduced GI villi damage compared to vehicle-treated subjects. Taken together the data suggests that promoting vascular stability following SCI by an IV administration of Ang-1 not only reduces GI vascular permeability but also appears to preserve intestinal villi.

Keywords: gastrointestinal, dynamic contrast enhanced imaging, vascular permeability

S12 Open Communication: Clinical

S12-01

A PROGNOSTIC MODEL FOR DETERMINING ONE-MONTH OUTCOMES IN MILD TRAUMATIC BRAIN INJURY

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There are currently no tools for aiding emergency physicians in educating mild traumatic brain injury (mTBI) patients regarding the prognosis of their injury. We sought to derive a model for identifying mTBI patients at risk for incomplete recovery from their symptoms at 1-month after injury. We analyzed data from a prospective cohort of TBI patients presenting to an urban emergency department (ED) (The ***Head*** injury ***S***erum ***M***arkers for ***A***ssessing ***R***esponse to ***T***rauma [HeadSMART] cohort). Subjects presenting within 24 hours of injury were interviewed on the day of injury. Telephone interviews were performed at 1-month after injury to determine TBI outcomes. Incomplete recovery was defined as Glasgow Outcome Scale Extended (GOSE) < 8. Prognostic models were built using univariable and multivariable logistic regression methods and stepwise selection procedures. A total of 194 subjects were enrolled between April 2014 and February 2015. Of this number, 108 were mTBI patients with a presenting Glasgow Coma Scale (GCS) of 14 or 15; a negative head CT scan; and 1-month follow-up data were included in this analysis. Within this subpopulation, 52.8% (57/108) had GOSE < 8 at 1 month. Predictor variables included in the final prognostic model were altered mental status at presentation (AMS), gender, race (African-American or non-African American), work-related injury, dangerous injury mechanism (ejection from motor vehicle, pedestrian struck, fall from height > 3ft or 5 stairs), and other injury (solid organ injury or bony fracture). This model discriminated between subjects with and without incomplete recovery with an area under the receiver operator curve (AUC) of 0.82 (95% CI: 0.73 – 0.88). A HeadSMART30 score was computed by assigning a score of 2 for AMS, 1 for female gender, 2 for

African-American, 2 for work-related injury, 1 for dangerous mechanism and 1 for other injury. Subjects with a HeadSMART30 < 7; 7 and 8; 9 and 10; and greater than 10 had a 1-month risk of incomplete recovery of 0%, 27%, 71% and 86% respectively. This study provides preliminary evidence that prognostication of mTBI outcome using readily available clinical and demographic data is feasible.

Keywords: prognostic models, GOSE, TBI

S12-02

AN INITIAL EVALUATION OF THE NINDS PHENOTYPING COMMON DATA ELEMENTS FOR TRAUMATIC BRAIN INJURY

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Introduction: In 2010, the NIH and other federal agencies identified a list of Common Data Elements (CDE) that might be used in traumatic brain injury (TBI) research. The selection of these instruments was not empirically based, but was guided by their availability in the public domain, the availability of alternate forms, and, most importantly, expert opinion regarding the utility of the tests. The present study undertakes an empirical examination of these instruments, comparing their performance to other tests.

Methods: A total of 111 (62% male) subjects who had sustained a closed head injury were seen at 30, 90, 180 and/or 365 days post injury. Subjects were administered eight of the ten original ''core'' neuropsychological CDE's, two ''core'' CDE's were replaced by equivalent ''supplemental'' measures. Subjects were also administered seven additional ''supplemental'' CDE's, as well as additional well validated, commonly used neuropsychological tests. The percentage of individuals classified as ''impaired'' (scoring less than one standard deviation below the mean) was calculated for each time point and by severity.

Results: Our cohort included 60 mild, 33 moderate, and 18 severe patients with TBI. Of the original CDE's, the Trail Making Tests (TMT) A and B and California Verbal Learning Test (CVLT-2) were the most sensitive, identifying impairment regardless of patient severity or time since injury. Other original CDE tests, such the Wisconsin Card Sort did not perform as well. In addition, some other tests, such as the Booklet Category Test, Sea Shore Rhythm Test, Controlled Oral Word Association Test, Grooved Pegboard, and Finger Tapping Tests consistently identified impairment, outperformed the original CDE's.

Conclusions: Only some of the current CDE's were useful in our cohort. These included: TMT A and B, BSI and CVLT-2. In addition, a number of tests not included as original CDE's demonstrated sensitivity in the evaluation of TBI subjects and are recommended for use in this population.

Keywords: Common Data Elements, Neuropsychological, Outcomes, Phenotyping

S12-03

ADOLESCENT TRAUMATIC BRAIN INJURY INCREASES ALCOHOL CONSUMPTION AND REWARD IN FEMALE MICE

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Traumatic brain injury (TBI) is inextricably and bidirectionally linked with alcohol use. Some estimates implicate alcohol intoxication in one-third to one-half of all TBI cases. Alcohol use following injury can reduce the efficacy of rehabilitation and greatly increase the chances for additional injury. Additionally, there is mounting evidence that TBI itself may be a risk factor for the development of alcohol use disorders. Finally, patients injured in childhood have poorer overall life outcomes and a much greater likelihood of developing substance abuse disorders. We used a standardized closed head injury to model mild traumatic brain injuries. We found that mice injured during adolescence but not during adulthood exhibited much greater alcohol self-administration in adulthood. Further, this phenomenon was limited to female mice as there was no effect of injury in males. Using behavioral testing, we determined that increased drinking behavior is mediated by alterations in the rewarding properties of alcohol and not sensory deficits from TBI. Environmental enrichment administered after injury reduced axonal degeneration and prevented the increase in drinking behavior. Additionally, brain derived neurotrophic factor gene expression, which was reduced by TBI, was normalized by environmental enrichment. Finally, an analysis of human data indicated that girls injured during early adolescence were much more likely to misuse alcohol as adults than were girls injured during other developmental epochs. Together these results suggest a novel model of alterations in reward circuitry following trauma during development.

Keywords: Alcohol, Adolescent Injury, Environmental Enrichment, BDNF, Inflammation, Concussion

S12-04

SINGLE EPISODE OF SEVERE AXONAL INJURY IN HUMANS IS ASSOCIATED WITH PATHOLOGY RESEMBLING CHRONIC TRAUMATIC ENCEPHALOPATHY

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Chronic traumatic encephalopathy (CTE) is a neurodegenerative disorder associated with repetitive mild traumatic brain injury (TBI). In CTE, abnormal *tau* proteins aggregate in a distinctive pattern of neurofibrillary tangles (NFTs) and astrocytic tangles favoring sulcal depths, perivascular regions and superficial neocortical layers. It has been suggested that these *tau* aggregates develop following axonal damage and/or impact-related mechanical stresses.

We analyzed postmortem brains from six schizophrenic patients who had undergone prefrontal leucotomy prior to 1953 and then lived at least another 40 years. Because leucotomy involves severing axons of the prefrontal cortex, this procedure represents a single TBI with severe axonal injury and no external cortical impact. We examined cortical tissues at the leucotomy sites, prefrontal and caudal frontal cortices and hippocampi. We compared these specimens to brains of six age-matched, non-leucotomized schizophrenics. We conducted immunohistochemistry using antibodies against abnormal *tau,* β-amyloid and astrocytes. We performed APOE genotyping for the six leucotomy patients.

In all six leucotomy cases, prefrontal lesion sites revealed severe white matter damage. Abnormal *tau* (NFTs and astrocytic tangles) was detected in cortex adjacent to leucotomy sites, involving depths of sulci, perivascular regions and superficial neocortical layers, but not in prefrontal and caudal frontal cortices distant to the leucotomy lesions. Similarly, β-amyloid plaques occupied the gray matter adjacent to the

lesion sites, but only in the three patients with APOEε4 haplotypes. Non-leucotomized schizophrenic patients showed no significant pathology.

Massive chronic axonal damage in white matter, as produced in leucotomy, leads to abnormal *tau* in neurons and astrocytes in gray matter adjacent to the lesion in the distinctive pattern resembling CTE. These data suggest that chronic neuronal deafferentation alone leads to abnormal *tau* accumulation. Because leucotomy lacks external cortical impact, the data suggest that selective accumulation of *tau* at depths of sulci may be related to underlying axonal damage rather than mechanical stresses during TBI. Lastly, only patients with the APOEε4 haplotype formed β-amyloid plaques.

Keywords: CTE, Axonal injury, tau, neuropathology

S12-05

TRAUMATIC AXONAL INJURY IN THE LIVING HUMAN BRAIN: CONCORDANCE OF MICRODIALYSIS AND ADVANCED MRI APPROACHES

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We performed microdialysis and diffusion tensor imaging in the same cohort of 15 severe traumatic brain injury patients to assess axonal injury with 2 complementary approaches. 100 kDa cut-off microdialysis catheters were implanted at a median time of 17 h (13–29 hours) after injury in normal appearing (on CT scan) frontal white matter in all patients. Diffusion tensor MRI scans at 3T were performed 2–9 weeks after injury in 11 patients. Stability of diffusion tensor imaging findings was verified by repeat scans 1–3 years later in 7 patients. An additional 4 patients were scanned only at 1–3 years after injury. Imaging abnormalities were assessed based on comparisons with 5 controls (healthy subjects) for each patient, matched by age and sex (32 controls in total).

We found that acute microdialysis measurements of the axonal cytoskeletal protein tau in the brain extracellular space correlated well with diffusion tensor MRI-based measurements of reduced brain white matter integrity in the 1 cm radius white matter-masked region near the microdialysis catheter insertion sites. Specifically, we found a significant inverse correlation between microdialysis measured levels of tau 13–36 hours after injury and anisotropy reductions in comparison with healthy controls (Spearman $r = -0.64$, $p = 0.006$). Anisotropy reductions near microdialysis catheter insertion sites were highly correlated with reductions in multiple additional white matter regions. We interpret this result to mean that both microdialysis and diffusion tensor MRI accurately reflect the same pathophysiological process: traumatic axonal injury. This cross-validation increases confidence in both methods for the clinical assessment of axonal injury. Future work will be required to determine the prognostic significance of these assessments of traumatic axonal injury when combined with other clinical and radiological measures.

Keywords: microdialysis, diffusion tensor imaging, tau

Poster Abstracts

A1 Poster Session I - Group A: Cell Death

A1-01

REPETITIVE PRIMARY BLAST-INDUCED VULNERABILITY AND DEFICITS IN LONG-TERM POTENTIATION WITHOUT CELL DEATH

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Introduction: Soldiers can experience 20 explosive detonations during 5 days of practical training and report symptoms of mild traumatic brain injury. It is unclear if primary blast (shock wave loading) increases the brain's vulnerability to subsequent injury resulting in worse outcomes.

Methods: Organotypic hippocampal slice cultures (OHSC) were generated from P8-10 rat pups. Shock waves of varying intensities (9, 39, or 87 kPa*ms) were generated with a shock tube. For repetitive blast studies, OHSC received 2 blasts 24 or 72h apart or 3 blasts within 10 minutes. Cell death was quantified as the percentage area of a specific region of interest (ROI) exhibiting propidium iodide (PI) fluorescence above a threshold on day 3 following final exposure. Electrophysiological function was evaluated by collecting stimulus-response (S-R) and long-term potentiation (LTP) data with microelectrode arrays on days 3–5 following final exposure. As a positive control OHSC were treated with glutamate (10 mM, 3 hours) following experimentation.

Results: There was a significant decrease in LTP for OHSCs receiving 2 blasts of 39 kPa*ms delivered 24h or 72h apart compared to sham. There was no significant difference in LTP among OHSCs receiving 1 blast of 39 kPa*ms or 1 or 2 blasts of 9 kPa*ms. There was a significant decrease in LTP for OHSCs receiving 1 blast of 87 kPa*ms. Cell death did not increase significantly following repetitive primary blast. The positive control indicated OHSC contained viable cells that were not killed by blast injury. There was no significant difference among OHSC receiving 0, 1, or 2 blasts of 37 kPa*ms for any S-R parameter.

Discussion: A single 39 kPa*ms blast initiated a period of heightened vulnerability that persisted for at least 3 days. The threshold for heightened blast-induced vulnerability was between 9 and 39 kPa*ms. Changes in LTP were observed in the absence of cell death or significant changes in cell firing. This suggests that primary blast and repetitive primary blast can damage mechanisms specific to LTP in the absence of gross structural damage to the hippocampus.

Keywords: Blast, Neuron

A1-02

INHIBITION OF RNA-POLYMERASE-1 PROTECTS OLIGODENDROCYTES AGAINST ENDOPLASMIC RETICULUM STRESS

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Recent work has documented that the conserved ER stress response (ERSR) is activated after contusive SCI and that its genetic or pharmacological modification protects white matter, prevents oligodendrocyte apoptosis and improves functional recovery after trauma. Ribosome is the nexus of protein synthesis. Ribosomal biogenesis takes place in the nucleolus where the RNA polymerase I (Pol1)-driven transcription of ribosomal RNA (rRNA) initiates that process. As cancer cells hijack ribosome biogenesis to fuel their growth, Pol1 became a target of novel anti-cancer drugs including the clinically tested CX-5461 or the recently identified BMH-21. Surprisingly, we found that ribosomal biogenesis is increased after moderate thoracic SCI and remains active in cultured oligodendrocytes precursor cells (OPC) that were challenged with ER stress inducers including tunicamycin or thapsigargin. Importantly, transient, non-toxic inhibition of ribosomal biogenesis using CX-5461 or BMH-21 protected mouse or rat OPCs against ER stress toxicity. The protection was accompanied by enhancement of the pro-survival phosphorylation of the eIF2alpha and moderate modulation of ER stress-mediated inhibition of general protein synthesis. Induction of the ER stress-related killer transcription factor CHOP was unaffected by Pol1 inhibitors. Instead, these agents activated p53 whose pharmacological inhibition blocked the anti-ER stress protection. Most interestingly, *i.p.* treatment with BMH-21 inhibited ribosomal biogenesis in the mouse spinal cord and increased expression of oligodendrocyte markers following SCI. These findings suggest that the nucleolar disruption and the subsequent activation of p53 support OPC and/or oligodendrocyte survival under conditions of ER stress.

Keywords: nucleolus, endoplasmic reticulum stress, oligodendrocytes

A1-03

USE OF AN IN VITRO MODEL TO STUDY THE ACUTE EFFECTS OF BLAST OVERPRESSURE ON NEURONS AND GLIAL CELLS

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Blast-induced traumatic brain injury (bTBI) is a significant cause of morbidity in US soldiers. Understanding the underlying mechanisms of cellular and molecular neuropathology in bTBI is essential for the development of effective treatments. This study characterized acute effects of blast overpressure in rat organotypic hippocampal slice cultures (OHCs). OHCs were exposed to a single blast overpressure of 150 or 280 kPa generated by an open-ended helium-driven shock tube. Cell death was visualized by the fluorescent cell death marker propidium iodide (PI). Co-labeling with the neuronal marker (neuronal class III β-tubulin; Tuj1), the microglial marker (ionized calcium-binding adapter molecule 1; Iba1), or the astrocyte marker (glial fibrillary acidic protein; GFAP) revealed the phenotype of cells susceptible to blast injury. At 2 h, following exposure to either blast overpressure, dead neurons and glial cells were observed. Additionally, in both blast groups we detected the presence of phagocytic microglia cells, suggesting their role in dead cell clearance. In previous studies, we demonstrated at 72 h post-injury the majority of dead cells were neurons while only few dead glial cells were observed at this later time point. Together, our results suggest the progression of blast-evoked cell death depends on the cell type. Specifically, microglia and astrocytes appear susceptible to blast overpressure in the acute phase, yet we do not observe the progression of cell death at 72 h post-injury. In contrast, neuronal loss progresses over time following blast exposure. Future studies will reveal potential correlations between the acute effects of blast on glial cells and delayed neuronal loss.

Supported by Department of Neurosurgery, MCW and VA Research

Keywords: blast injury, hippocampus, organotypic slice culture, traumatic brain injury

A1-04

INHIBITION OF CA^{2+}-INDEPENDENT PLA2γ EXACERBATED THE MECHANICAL STRETCH INJURY IN PRIMARY CORTICAL NEURONS

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Ca^{2+}-independent $PLA_2\gamma$ ($iPLA_2\gamma$), known as Group VIA PLA_2, hydrolyze phospholipids at the sn-2 position, thereby releasing free fatty acids and a lysophospholipids. In some studies found $iPLA_2\gamma$ not only like other PLA_2 releasing FFAs to regulate inflammation, but also have key role in membrane phospholipid metabolism and remodeling especially under oxidative stress. And the location of $iPLA_2\gamma$ is on endoplasmic reticulum and mitochondria. This implies that $iPLA_2\gamma$ may participate the membrane phospholipid injury and repair when mitochondria under oxidative stress. And previously, we found that selective peroxidation of mitochondria membrane phospholipid cardiolipin as an important pathogenic mechanism for TBI. So we use (R)-BEL, a specific inhibitor of $iPLA_2\gamma$, to clarify the role of $iPLA_2\gamma$ when under mitochondrial oxidative stress damage after stretch in primary cortical neurons. In the current report, we found that $iPLA_2\gamma$ inhibitor deteriorate the mechanical stretch injury. Cytochrome c is released into the cytoplasm and caspase3 apoptosis pathway is activated. And we found mechanical stretch damage the mitochondrial membrane potential, and $iPLA_2\gamma$ inhibitor aggravated the damage. The inhibition of $iPLA_2\gamma$ may increase the mitochondrial apoptosis and injury. Furthermore, MDA,4-HNE, products of lipid peroxidation, increase after stretch, and $iPLA_2\gamma$ inhibitor exacerbated the lipid peroxidation. And $iPLA_2\gamma$ inhibitor also increased stretch-induced ROS production by DCFH-DA staining. Interestingly after stretch $iPLA_2\gamma$ expression level did not change significantly, but $iPLA_2\gamma$ activity significant increased. Our result suggested that $iPLA_2\gamma$ is neuroprotective and $iPLA_2\gamma$ can be up-regulated to relieve the mitochondrial injuries. And this protective effect may via mitochondrial membrane phospholipid remodeling pathway. Further detailed mechanism about the $iPLA_2\gamma$ after stretch needs to be clarified.

Keywords: Ca^{2+}-independent PLA2γ, mitochondria, oxidative stress, lipid peroxidation

A1-05

A NOVEL METHOD FOR TRAUMATIC INJURY OF ORGANOTYPIC HIPPOCAMPAL SLICE CULTURES

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Background: Organotypic hippocampal slice cultures (OHSC) can be used to model molecular changes after traumatic brain injury. Previous OHSC models of traumatic injury have used proprietary equipment. We report a novel method of inducing mechanical injury in OHSC using a commercially available device.

Methods: Briefly, 400-micrometer slices were prepared from hippocampi from P5-7 C57Bl6 mice and placed on Bioflex plates (Flexcell Int) coated with polyornithine and laminin. Slices were incubated on a rocker until DIV10. Culture medium was changed to artificial cerebrospinal fluid with propidium iodide (PI). Images were obtrained from a Zeiss Axiovert microscope with a custom-built stage adapter and rhodamine filter. The Cell Injury Controller II (Custom Design and Fabrication, VA) stretched OHSC with pulse duration 80 msec and varied injury pressures (3.3 to 7.6 PSI). Images were recorded at 2, 6, 12, and 24 hours post-injury. Slices were treated with sucrose overnight to determine maximum PI uptake. Fluorescence intensity was measured (Image J). Fractional PI uptake was calculated to quantify cell death (1.0 = maximum cell death).

Results: Control slices demonstrated low baseline PI uptake after 24h (CA1 0.11 ± 0.03, mean $\pm$ SD). Fractional PI uptake was altered for CA1, CA3, and DG regions after stretch injury at 24h ($p < 0.001$, ANOVA). PI staining at low levels of stretch was not significantly different than control OHSC (3.5 PSI:0.11 ± 0.03; 4.1 PSI:0.14 ± 01; 4.4 PSI:0.17 ± 0.04; p NS). Maximum PI uptake occurred at injuries above 5.2 PSI (0.31 ± 0.05). Additional PI uptake did not occur with higher pressures (6.4 PSI: 0.32 ± 0.04, 7.4 PSI: 0.29 ± 0.04). In CA1, control values differed from 5.2 PSI, 6.4 PSI, and 7.4 PSI ($p < 0.01$ for all, Dunn's). Mild stretch injury (3.3 PSI, 4.4 PSI) differed from severe stretch injuries (5.2 PSI, 6.4 PSI, $p < 0.01$). Other hippocampal regions (CA3, DG) showed similar patterns of cell death.

Conclusions: Our methods yielded consistent, reproducible injury to neuronal regions in OHSC. This model can be used to study effects of varying ACSF constituents or screening therapeutic agents in isolated brain tissue.

Keywords: Tissue Culture, Hippocampus, Artificial Cerebrospinal Fluid

A1-06

DISRUPTED AUTOPHAGY AFTER SPINAL CORD INJURY IS ASSOCIATED WITH ER STRESS AND NEURONAL CELL DEATH

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Autophagy is a catabolic mechanism facilitating degradation of cytoplasmic proteins and organelles in a lysosome-dependent manner. Autophagy flux is necessary for normal neuronal homeostasis and its dysfunction contributes to neuronal cell death in several neurodegenerative diseases. Although signs of elevated autophagy have been reported after SCI, its mechanism, cell type specificity, and relationship with cell death remain unknown.

In a rat model of contusive SCI, we observed accumulation of LC3-II positive autophagosomes starting at post-trauma day 1. This was accompanied by a pronounced accumulation of autophagy substrate protein p62/SQSTM1, indicating that early elevation of autophagy markers reflects disrupted autophagosome degradation. Levels of lysosomal protease cathepsin D (CTSD) and numbers of CTSD positive lysosomes were also decreased at this time, suggesting that lysosomal damage may contribute to the observed defect in autophagy flux. Normalization of SQSTM1 levels started by day 7 after SCI, and was associated with increased CTSD levels. Therefore, increase in the size and activity of the lysosomal compartment may eventually help restore autophagy flux.

At day 1 after SCI accumulation of autophagosomes was most pronounced in ventral horn motor neurons and dorsal column oligodendrocytes and microglia. In motor neurons disruption of autophagy strongly correlated with evidence of endoplasmic reticulum (ER) stress. As autophagy is thought to protect against ER stress, its disruption after SCI could contribute to ER stress-induced neuronal apoptosis. Consistently, motor neurons showing disrupted autophagy co-expressed ER-stress associated initiator caspase 12 and cleaved executioner caspase 3. Together these findings indicate that SCI causes lysosomal dysfunction that contributes to disruption of autophagy flux and associated ER stress-induced neuronal apoptosis.

Keywords: autophagy, ER stress, apoptosis, lysosome, rat contusive SCI

A1-07

LYSOSOMAL DAMAGE LEADS TO INHIBITION OF AUTOPHAGY AND CONTRIBUTES TO NEURONAL CELL DEATH AFTER TBI

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Disruption of autophagy, a lysosome-dependent intracellular degradation process, has been implicated in both acute and chronic neurodegenerative diseases. Although increase in markers of autophagy has been reported in the brain after traumatic brain injury (TBI), its cell type specificity, mechanisms and function remain unknown.

Following controlled cortical impact (CCI) brain injury in *GFP-LC3* transgenic mice, we observed accumulation of autophagosomes in the ipsilateral cortex and hippocampus starting by 24 hours after injury. This accumulation was not due to increased initiation of autophagy but rather to decrease in clearance of autophagosomes, as reflected by accumulation of SQSTM1/p62. This was confirmed by *ex vivo* studies demonstrating impaired autophagy flux in brain slices from injured as compared to control animals. The impairment of autophagy was at least in part caused by TBI-induced decrease in lysosomal function, evidenced by lower protein levels and enzymatic activity of cathepsin D (CTSD) in the injured cortex. CTSD was also abnormally localized to the cytosol after TBI, suggesting that lysosomal dysfunction was caused by injury-induced lysosomal membrane permeabilization.

At 1 day after TBI autophagy flux was inhibited predominantly in neurons. At that time we observed co-localization of GFP-LC3 signal with markers of caspase dependent (cleaved caspase 3, caspase 12) and caspase-independent (AIF) cell death, indicating that inhibition of the autophagy-lysosomal pathway contributes to neuronal cell death. Taken together, our data demonstrate that autophagic clearance is compromised after TBI due to injury-induced lysosomal damage and likely contributes to neuronal cell death. Autophagic flux was restored by day 7, at which point autophagy could become neuroprotective. We propose that restoration of lysosomal function and autophagy flux may represent novel therapeutic strategies to limit neuronal loss after TBI.

Keywords: autophagy, lysosome, transgenic mouse, CCI, injury mechanisms

A1-08

SILICONE PAD DEMONSTRATES SIMILAR LEVEL OF EFFECTIVENESS AS NEOPRENE PAD ON FLUID PERCUSSION INJURY DEVICE

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Introduction: Traumatic brain injury (TBI) affects millions of American civilians and military service personnel. One of the models used to study TBI is the fluid percussion injury device (FPI). Traditionally, a neoprene pad has been used on the end of the plunger of the FPI device. We tested a silicone-based pad to determine if it would produce injury levels similar to that of the neoprene pad.

Methods: Male Sprague Dawley rats were anesthetized, intubated, mechanically ventilated and prepared for FPI. Animals were randomly assigned to receive sham, moderate FPI with neoprene pad (nFPI) or moderate FPI with silicone pad (sFPI). Anesthesia was discontinued and, upon return of a withdrawal reflex in response to paw pinch, animals received FPI. Return of righting reflex (RR) time measurements commenced immediately upon injury. Animals survived for 24 hours prior to being euthanized and their brains were collected and fresh-frozen. Ten coronal (10 mM thickness) sections were collected every 15th section throughout the injury site. Sections were stained with .001% Fluorojade-C (FJ), and positive cells were counted in the CA1/2 and CA3 regions of the hippocampus by two blinded investigators.

Results: Overall, there were no statistically significant differences between the two pad materials used on the FPI device when delivering moderate (2.0 atm) severity levels. There was a significant correlation between the RR measurements and the numbers of FJ-positive (injured) neurons in the rat hippocampus. We conclude from these data that the silicone and neoprene pads deliver a similar level of injury and either can be used on the FPI device.

These studies were completed as part of an interdisciplinary research team funded by The Moody Project for Translational Traumatic Brain Injury Research.

Keywords: fluid percussion, model comparison, righting reflex, cell death

A1-09

PROTECTIVE EFFECTS OF ESTROGEN IN VASCULAR SMOOTH MUSCLE CELLS AFTER RAPID-STRETCH INJURY

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Reduced cerebral blood flow (CBF) and impaired compensatory cerebral vascular responses to reduced arterial blood pressure after TBI may contribute to life-long disability or death. Cerebrovascular effects of TBI are mediated in part by disruption of gap junctions (GJs), low resistance channels between adjacent cells (Yu, et al., JNT, 2014). The neuroprotective effects of estrogen are due, in part, to the maintenance of adequate perfusion after TBI (Roof & Hall, JNT, 2000) but the effects of estrogen on GJ function after vascular injury are unknown. We examined the effects of 17-beta estradiol (E2) on intracellular calcium (Ca^{++}) and reactive oxygen species (ROS) levels and gap junction (GJ) communication in vascular smooth muscle (VSM) cells subjected to rapid stretch injury (RSI), an *in vitro* model that replicates many features of TBI *in vivo*. Rat VSM cells were subjected to RSI (30, 40, 50 psi for 50 ms) and treated with vehicle or E2 (80 nM) for 30 min immediately post-injury. Intracellular Ca^{++} levels were measured with Fura-4/AM. Intracellular ROS levels were measured with 5,6-Chloromethyl-2′,7-dichlorodihydrofluorescein diacetate acetyl, mixed isomers (CM-H2DCFDA). To assess GJ coupling, cells were loaded with 5,6-CFDA/AM and fluorescence recovery after photobleaching was measured. In the cells subjected to RSI and treated with E2, intracellular Ca^{++} and ROS levels were reduced significantly ($P < 0.01$ RSI E2 vs. RSI vehicle). GJ coupling also was significantly ($P < 0.05$ RSI E2 vs. RSI vehicle). Our results that post treatment with E2 reduced intracellular ROS and Ca^{++} levels while improving GJ coupling after RSI suggest that E2 protection of GJ coupling may be mediated through reductions in intracellular ROS and Ca^{++}. *These studies were supported by The Moody Project for Translational TBI Research.*

Keywords: estrogen, intracellular calcium, reactive oxygen species, intercellular gap junction, Neuroprotection

A2 Poster Session I - Group A: Secondary Injury

A2-01

SAFETY, TOLERABILITY, AND EFFECTIVENESS OF DEXTROMETHORPHAN/QUINIDINE FOR PSEUDOBULBAR AFFECT IN TRAUMATIC BRAIN INJURY: PRISM-II

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Pseudobulbar affect (PBA) is characterized by frequent, uncontrollable episodes of crying and/or laughing that are exaggerated or incongruous with mood or social context and can occur secondary to a variety of unrelated neurologic conditions. A multicenter, open-label study (PRISM-II) assessed the effectiveness, safety, and tolerability of dextromethorphan and quinidine (DM/Q) combination for the treatment of PBA in patients with stroke, dementia, or traumatic brain injury (TBI). This was a 12-week, US multicenter, open-label trial of DM/Q for the treatment of PBA. All eligible patients from the TBI cohort had a clinical diagnosis of PBA, a Center for Neurologic Study-Lability Scale (CNS-LS) score ≥13 (range 7–35), and a clinical diagnosis of non-penetrating TBI, which was stable and non-evolving. Patients with unstable medical illness or contraindications to DM/Q were excluded. Enrolled patients received DM 20 mg/Q 10 mg twice daily for 12 weeks (once daily in week 1). Concomitant mood/behavioral medications were allowed if stable for ≥2 months. The primary endpoint was change in CNS-LS score from baseline to Day 90/early withdrawal. Additional endpoints included the change in PBA episodes/week, QOL Visual Analogue Scale (VAS), Clinical and Patient Global Impression of Change (CGI-C and PGI-C), Mini-Mental State Examination (MMSE), the TBI Neurobehavioral Functioning Inventory (NFI), patient treatment satisfaction, and the Patient Health Questionnaire (PHQ-9) assessing depressive symptoms. Vital signs and adverse events were monitored throughout. Enrollment in the PRISM-II TBI cohort (n = 120) has completed (last patient out April 2015). Final results will be available and presented. PRISM-II is the first prospective open-label study to systematically evaluate DM/Q safety, tolerability, and effectiveness in patients with PBA secondary to TBI as well as the impact of symptom relief on health-related outcomes. Study supported by: Avanir Pharmaceuticals, Inc.

Keywords: pseudobulbar affect, affective symptoms, quinidine- dextromethorphan combination, brain injuries, quality of life, depression

A2-02

DOES A HIGHER HEMOGLOBIN TRANSFUSION THRESHOLD AFFECT THE RISK OF PROGRESSIVE HEMORRHAGE AFTER SEVERE TRAUMATIC BRAIN INJURY?

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Maintenance of a higher hemoglobin threshold after severe TBI can increase the risk of delayed mortality. The objective of this study was to determine if maintaining a higher hemoglobin transfusion threshold was associated with an increased incidence of progressive hemorrhage after severe TBI. Data was obtained from a recently performed prospective randomized clinical trial studying the effects of erythropoietin and blood transfusions on neurological recovery after severe TBI. We defined progressive hemorrhage as the presence of new or enlarging intracranial hematomas on computerized tomography up to 24 hours after injury. Severe progressive hemorrhage included events that required an escalation of medical management or surgical intervention. Multivariate Cox regression analysis was used to identify independent risk factors for progressive hemorrhage after severe TBI. Progressive hemorrhage was detected on CT imaging in 61 severe TBI patients (30.5%). The commonest finding was a new, delayed contusion (n = 30, 49.2%). Progressive hemorrhage was identified at a mean duration of 17.2 ± 15.8 hours after injury. Ninety-nine patients were assigned a transfusion threshold of 7 g/dl, and 101 patients were assigned a transfusion threshold of 10 g/dl. Patients with a transfusion trigger of 10 gm/dl had a higher risk of severe progressive hemorrhage (Hazard ratio 2.3, 95% CI 1.1–4.7, p = 0.02). Factors that decreased the risk of severe progressive hemorrhage included surgery on admission and diffuse brain injury, while factors such as higher initial ICP increased the risk of severe progressive hemorrhage. A higher transfusion threshold of 10 g/dl after severe TBI increased the risk of severe PHI events, and these results indicate the potential adverse effect of maintaining a higher hemoglobin transfusion threshold after severe TBI.

Keywords: transfusion, traumatic brain injury, progressive hemorrhagic injury, decompressive craniectomy

A2-03

THE ROLE OF 7,8-DIHYDROXYFLAVONE IN PREVENTING DENDRITE DEGENERATION IN CORTEX AFTER MODERATE TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) is a serious public health problem in the United States (US). TBI is a contributing factor to a third (30.5%) of all injury-related deaths in the US. Every year, at least 1.7 million TBIs occur either as an isolated injury or along with other injuries. In 2010, the total of direct and indirect medical costs was an estimated $80 billion. Our previous research showed that traumatic brain injury (TBI) induced by controlled cortical impact (CCI) causes not only massive cell death, but also results extensive dendrite degeneration in those spared neurons in the cortex. Cell death and dendrite degeneration in the cortex may contribute to persistent cognitive, sensory, and motor dysfunction. There is still no approach available to prevent cells from death and dendrites from degeneration following TBI. When we treated the animals with a small molecule, 7,8-Dihydroxyflavone (DHF) that mimics the function of BDNF through provoking TrkB activation, reduced dendrite swellings in the cortex. DHF treatment also prevented dendritic spine loss after TBI. Functional analysis showed that DHF improved rotarod performance on the third day after surgery. These results suggest that DHF treatment significantly prevented dendrites from degenerating, and protected dendritic spines against TBI insult. Consequently, DHF can partially improve the behavior outcomes after TBI.

Keywords: Traumatic brain injury, dendrite, degeneration, brain-derived neurotrophic factor, 7,8-dihydroxyflavone

A2-04

PROFILE OF PHOSPHOLIPID ALTERATIONS OF SPINAL CORD INJURY: LIPIDOMIC ANALYSIS

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Although phospholipid alteration has long been associated with spinal cord injury (SCI), its profile and specific role in mediating damage is not well understood. In this study, we investigated alteration of phospholipids with an emphasis on cardiolipin (CL), in the adult rat spinal cord following a T10 contusive injury using an IH impactor (175 kdyne). Mass spectrometry-based lipidomic analysis showed a significant decrease in CL, sulfatide, phosphatidylinositol and phosphatidylcholine as well as a significant increase in lyso-cardiolipin (lyso-CL), lyso-phosphatidylcholine and acylcarnitine after SCI. CL is emerging as an important player in the control of the mitochondrial phase of apoptosis. The content of CL was found to be significantly reduced at 3 and 24 h after SCI while lyso-CL was increased only at 24 h after the injury. Over 50 distinct CL molecular species were readily identified. Of them, 50% were significantly reduced after SCI. These reduced CL species mainly contain polyunsaturated arachidonic acid ($C_{20:4}$)(AA), docosahexaenoic acid ($C_{22:6}$)(DHA), and linoleic acid ($C_{18:2}$)(LA) fatty acids that are highly susceptible to peroxidation. Additionally, 4-HNE, a marker of lipid peroxidation, also increased at 3 and 24 h after SCI. These findings suggest that CL underwent oxidation and hydrolysis after SCI. *In vitro* experiments showed that cytosolic phospholipase A_2 ($cPLA_2$) activation induced CL loss. *In vivo* experiments showed that mitochondrial $cPLA_2$ activation was increased after SCI. Remarkably, blocking $cPLA_2$ pharmacologically with AACOCF3 in rats or genetic deletion of $cPLA_2$ in mice reduced CL loss, mitochondrial dysfunction, cytochrome c release, and neural apoptosis after SCI. These findings collectively suggest that CL alteration is an early response following SCI and that such CL alteration is mediated by oxidative stress and $cPLA_2$ activation. Thus, CL alteration may play an important role in the pathogenesis of SCI, and as such could be an attractive therapeutic target for ameliorating secondary SCI.

Keywords: spinal cord injury, cardiolipin, cPLA2, apoptosis

A2-05

DOES THE PLASMINOGEN ACTIVATION SYSTEM REGULATE POST-TRAUMATIC DEMENTIA?

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Young adults with a medical history of moderate to severe brain trauma have an increased risk of developing Alzheimer disease (AD), Lewy body disease- like pathology and Chronic traumatic encephalopathy (CTE). The plasminogen activating (PA) system facilitates breakdown of blood clots in the circulation, but also regulates extracellular activities in the brain. tPA is a protease that cleaves plasminogen to generate plasmin, which facilitates clot removal. tPA activity is down-regulated by α-synuclein, a protein that accumulates in Lewy bodies. Clearance of exogenous Aβ is significantly slower in mice lacking tPA or plasminogen, confirming that the tPA–plasmin system is involved in Aβ degradation. We have previously shown that plasmin deficiency leads to enhanced accumulation of aggregated tubulin after trauma. We investigated whether plasmin deficient mice are more susceptible to accumulation of amyloid-β leading to dementia-related pathology with 24–72h post-trauma. Our data shows that deficiency of plasmin does not result in an increased post-traumatic accumulation amyloid-β within this timeframe and does not promote cognitive dysfunction over a longer-term period. We quantitated amyloid-β, Tau and α-synuclein in post-mortem brain tissue of TBI and non-TBI patients. We found an increase in amyloid-β as well as oligomeric α-synuclein within one-week post-TBI. Preliminary analysis shows that amyloid burden was increased in patients who had the 7351C/T polymorphism in the tPA gene, that results in a decrease in tPA activity. Therefore the PA system may have a role in regulating the onset of dementia-like pathology after trauma. However it is likely that tPA-mediated clearance of aggregated proteins may occur via plasminogen-dependent and independent mechanisms.

Keywords: plasminogen activation system, amyloid beta, alpha synuclein, tissue plasminogen activator

A2-06

THE PERFLUOROCARBON NVX-108 INCREASED BRAIN TISSUE OXYGENATION AFTER CONTROLLED CORTICAL IMPACT BRAIN INJURY IN THE RAT

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Hypoxia is a critical secondary injury mechanism in traumatic brain injury (TBI), and early intervention to alleviate post-TBI hypoxia may be beneficial. NVX-108 (NuvOx Pharma, Tucson, AZ), a dodecafluoropentane perfluorocarbon, was screened for its effect on brain tissue oxygenation ($PbtO_2$) when administered soon after TBI. Anesthetized rats ventilated with 40% oxygen underwent moderate controlled cortical impact (CCI) TBI at time 0 (T0). Rats received either no treatment (NON, n = 8) or 0.5 ml/kg intravenous (IV) NVX-108 (NVX, n = 9) at T15 (15 min after TBI) and T75. Brain tissue oxygenation was measured non-invasively using phosphorescence quenching method (PQM). After CCI-TBI, $PbtO_2$ dropped by $48 \pm 6\%$ ($p < 0.001$) in the NVX group and by $46 \pm 5\%$ ($p < 0.001$) in the NON group compared to baseline. Throughout the rest of the study period (155 min) $PbtO_2$ in the NON group never recovered and remained at the immediate post-injury level (16 ± 2 mm Hg). In NVX group, NVX-108 infusion resulted in a steady increase in $PbtO_2$, and at T115 it recovered to pre-injury values. At T135, $PbtO_2$ was significantly higher ($p < 0.05$) compared to post-injury values. This increase in PbtO2 was maintained until the end of the study. No changes were noted in hemodynamics, body temperature, acid-base balance, electrolytes or hemoglobin concentration. In conclusion, the perfluorocarbon NVX-108 caused an increase in $PbtO_2$ following moderately severe CCI-TBI in rats and should be evaluated further as a possible immediate treatment for TBI.

Keywords: PbtO2, oxygen therapeutics, phosphorescence, PFC

A2-07

OXYGEN CARRIER M-101 DID NOT CAUSE VASOCONSTRICTION AND IMPROVED CEREBRAL OXYGENATION AFTER TBI IN RATS

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The severity of traumatic brain injury (TBI) may be reduced if oxygen can be rapidly provided to the injured brain. This study evaluated if the oxygen-carrier M-101 (Hemarina, France) causes vasoconstricton of pial vasculature in healthy rats (experiment 1) and if it improves brain tissue oxygen ($PbtO_2$) in rats after controlled-cortical impact (CCI)-TBI (experiment 2). Experiment 1: M-101 was infused at 12.5 ml/kg IV over 2 h into anesthetized, healthy rats. Intravital microscopy was used to assess pial artery diameter over time. There was a mild (9 mm Hg) increase in the mean arterial blood pressure (MAP) without constriction of pial arterioles. Experiment 2: Anesthetized rats underwent CCI-TBI. 15 min after injury M-101 was infused IV (12 ml/kg over 1 h). Brain tissue oxygenation was assessed non-invasively via phosphorescence quenching method (PQM). In both M-101 and untreated control (NON) groups, $PbtO_2$ was $\sim 30 \pm 2$ mm Hg pre-injury and decreased ($P \leq 0.05$) to $\sim 16 \pm 2$ mm Hg 15 min after CCI. In the NON group, $PbtO_2$ remained $\sim 50\%$ of baseline until the end of the study. M-101 administration resulted in a sustained increase in $PbtO_2$ (peak: 25 ± 5 mm Hg), which elevated $PbtO_2$ to pre-injury values. At the end of the 155 min observation period, $PbtO_2$ slowly decreased below pre-injury levels, but was still higher than the NON group. Histopathology showed no differences between groups, possibly due to the short study duration. In conclusion, M-101 increased systemic blood pressures without concurrent cerebral pial vasoconstriction (in healthy rats) and restored $PbtO_2$ to 86% of pre-injury for at least 80 min when given soon after CCI-TBI. M-101 should be evaluated in a clinically relevant large animal model for pre-hospital treatment of TBI.

Keywords: hemoglobin-based oxygen carrier, oxygen therapeutic, pial microcirculation, brain oxygenation, controlled cortical impact

A2-08

TREATMENT AND RISK FACTORS FOR POST-TRAUMATIC EXTERNAL HYDROCEPHALUS FOLLOWING DECOMPRESSIVE CRANIECTOMY

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Objectives: Both external hydrocyphalus and simple subdural hygroma following decompressive craniectomy (DC) have been observed in a variety of traumatic brain injury (TBI) patients. In the early stage of most external hydrocyphalus cases, subdural fluid collection is the only significant signs on CT scans. Therefore, it is difficult to different early-stage external hydrocyphalus from simple subdural hygroma, resulting in inappropriate treatment and poor prognosis. In this study we assessed the risk factors for the development of external hydrocyphalus after DC, and the treatment strategies were also discussed.

Methods: A retrospective analysis was undertaken of TBI patients treated with DC at The Second Affiliated Hospital, Zhejiang University between January 2012 and December 2013. Risk factors for hydrocephalus were evaluated by using logistic regression analysis.

Results: Sixty-one patients with subdural fluid collection after DC were included in this study. Twenty cases developed clinical evidence of hydrocyphalus and required a ventriculoperitoneal shunt (VPS). Intraventricular hematoma ($p = 0.009$), interhemispheric hygroma ($p = 0.003$) and the onset time of sudural fluid collection ($p = 0.006$) were independent risk factors for external hydrocyphalus after DC. VPS and early cranioplasty were effective for external hydrocephalus patients.

Conclusions: Our results suggested that intraventricular hematoma, interhemishperic hygroma and onset time of subdural fluid collection could be predictors for external hydrocephalus after DC. Early cranioplasty and VPS not subdural peritoneal shunt should be considered for this clinical entity.

Keywords: Traumatic Brain Injury, Hydrocephalus, Subdural Hygroma, Decompressive Craniectomy

A2-09

THE INCIDENCE RATE OF MILD TRAUMATIC BRAIN INJURY IN PATIENTS SUFFERING FROM AN UPPER OR LOWER LIMB FRACTURE

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Orthopaedic traumas (e.g., limb fractures) typically caused by accidental falls or traffic road accidents generally require immediate surgical intervention. Loss of articular amplitude and motor weakness persist in some patients with no apparent anatomical abnormalities. Interestingly, mild traumatic brain injury (mTBI) present similar sequelae suggesting a connection between the two. Hence, it is possible that the severity of the fracture silence the otherwise apparent symptoms of mTBI, therefore preventing early detection. This study compares the incidence of concomitant mTBI detected at follow-up visits in a Level I Trauma Hospital's orthopaedic clinic with the incidence held by the hospital records. This study also seeks to determine which types of fractures and accidents present the highest incidence of mTBI.

Methods: 150 orthopaedic monotrauma patients were retrospectively assessed for mTBI through standardized semi-structured interviews.

Results: The incidence rate of mTBI accompanying upper limb fractures was 28% and 24% for lower limb fractures compared to the hospital incidence rates of 22% and 9%, respectively. Collarbone fractures presented the highest incidence rate with 64%. Among all types of accidents, high velocity accidents (e.g., traffic road accidents) presented the highest incidence rate with 79% compared to low velocity accidents (e.g., accidental falls) that showed an incidence rate of 11%.

Conclusion: Although preliminary, results suggest that a high rate of mTBI is undiagnosed in orthopaedic trauma patients, especially with lower limb fractures. Finally, the results reveal the importance of accounting for both the type of fracture and the type of accident, as incidence rates vary greatly.

Keywords: Mild traumatic brain injury, Orthopaedic Trauma, Incidence rate

A2-10

CALCIUM AND GLUTAMATE SIGNALING AFTER TBI VISUALIZED IN-VITRO USING GENE-ENCODED MOLECULAR SENSORS GCAMP6 AND IGLUSNFR

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An estimated 3.6 million Americans experience traumatic brain injury (TBI) annually, and effective treatments to improve neurological outcome following TBI are not yet available. Development of successful interventions requires a better understanding of the cellular mechanisms that lead to cell death and impaired neural function. Altered calcium and glutamate signaling are among the many sequelae associated with TBI, contributing to secondary cell injury and death. In addition, voltage gated calcium channels (VGCCs), including N-type VGCCs, play a critical role in the rise in intracellular calcium and the activation of calcium-dependent pathways leading to neuronal injury and death. However, previous data related to changes in calcium levels after TBI have come from acute studies using 45Ca autoradiography, ion-selective microelectrodes and calcium-sensitive dyes (e.g., Fura-2). Such techniques do not provide longitudinal information on changes in calcium levels that occur over the hours to days following TBI. Therefore, we initiated a series of studies using gene encoded molecular sensors (GEMS) that allow for long-term and repeated calcium and glutamate imaging *in vitro* and *in vivo*. We used the GEMS GCamP6 to visualize intracellular neuronal calcium-signaling in an *in vitro* model of TBI, imaging the same cells over 48 hours. Following injury there was a rapid rise in intracellular calcium that returned to near baseline levels over 48 hours. SNX-185, a synthetic ω-conopeptide and VGCC blocker, reduced the frequency and amplitude of calcium spikes prior to injury, and reduced calcium accumulation post-injury. Longitudinal imaging of calcium and glutamate in the same cells over extended periods of time using GEMS will allow better characterization of the pathophysiology of TBI. The technology also provides a high-throughput screening platform for compounds that may have therapeutic potential in the treatment of TBI.

Keywords: Gene Encoded Sensors, Longitudinal, Voltage Gated Calcium Channel Blockers

A2-11

A "NEET" MITOCHONDRIAL TARGET FOR TBI: THE IMPORTANCE OF MITONEET IN PIOGLITAZONE MEDIATED NEUROPROTECTION

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Traumatic Brain Injury (TBI) is difficult to treat due to the complicated secondary injury cascade that ensues following the initial insult. The most promising therapeutics are multi-targeted, improving neuroinflammation, ROS production and mitochondrial dysfunction. Pioglitazone, an FDA approved drug for Type 2 Diabetes and known PPAR agonist, has shown promise in altering neuroinflammation and decreasing ROS production. Work from our lab found that pioglitazone can increase mitochondrial bioenergetics within the first 12 to 24 hours post-injury. This effect, too rapid to be mediated through PPAR alone, may be dependent on its ability to bind a novel mitochondrial protein called mitoNEET. Therefore, we hypothesize that pioglitazone is a mitoNEET specific ligand that binds mitoNEET to improve mitochondrial bioenergetics leading to increased cortical sparing and functional recovery. To test this hypothesis we used a severe Controlled Cortical Impact (CCI) injury model, mitoNEET null and wild-type mice, pioglitazone and a novel mitoNEET ligand called NL-1, which is a truncated analogue of pioglitazone with no PPAR binding region. When simulating Ca^{2+} induced excitotoxicity, pioglitazone can increase bioenergetics in naïve isolated cortical mitochondria following insult with Ca^{2+} ($n=3$; $p<0.05$). An *in-vivo* pioglitazone ($n=9$) and NL-1 ($n=4$) dose-response study was then preformed in wild-type mice post-injury. The dosages with the greatest amelioration of mitochondrial dysfunction were used in wild-type and mitoNEET null mice following a sham or severe CCI surgery. At these dosages, pioglitazone lost its ability to increase mitochondrial respiration ($n=3$) and provide neuroprotection ($n=6$) in mitoNEET null mice. Additionally, NL-1 decreased MRI T2-weighted hyperintensity at the injury site and increased cortical sparing ($n=6$, $p=0.03$) and

motor recovery ($n = 16$, $p < 0.05$) following injury. These results shed light on the importance of mitoNEET as a novel target for the treatment of TBI and as a necessary protein in pioglitazone mediated neuroprotection.

Keywords: mitochondria, mitoNEET, pioglitazone, NL-1, Controlled Cortical Impact (CCI)

A2-12

DANTE: DEFORMITY, ANKYLOSIS, NEUROLOGIC DEFICIT, TRANSLATION, EXTENSIVE TRAUMA. A MNEMONIC PREDICTING SPINAL INSTABILITY

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Clinical evaluation of thoracolumbar trauma requires a complex understanding of spinal anatomy and mechanism of injury in order to determine stability. Numerous classification systems exist; however, each has limitations that risk potential missed diagnoses, progressive instability, and neurologic compromise. The limitations include poor reliability and repeatability, non-inclusion of comprehensive bodily survey, oversimplification, and failure to consider late mechanical and neurologic instability.

Thus; a comprehensive system that is relatively simple to recall and apply which incorporates basic modalities of patient evaluation including history, physical examination, and imaging is needed to help surgeons and non-surgeons in the decision making process.

A review of the literature revealed a core set of elements that may predict and determine thoracolumbar spinal stability. These elements can be summarized by the mnemonic **DANTE:**

D: Deformity – Radiographic criteria that can be observed on plain films; CT, or MRI. Greater than 15 to 25 degrees of kyphosis or 14 degrees of scoliosis is associated with discoligamentous instability. (McAfee)

A: Ankylosis, Age – Preexisting osseous disorders, such as ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis, or osteoporosis may also affect treatment decisions and initiate further imaging studies. Younger patients have ligamentous laxity; whereas, older patients bones are brittle.

N: Neurologic Injury – New neurologic deficit, even despite normal plain films or computerized tomography, should be evaluated further for discoligamentous instability. (Bradford, McBride)

T: Translation – Subluxation of adjacent segments of 10% or 4 mm in either the sagittal or coronal plane is associated with discoligamentous instability. (White, Panjabi)

E: Extensive Trauma –Traumatic injuries other than those involving the TL spine such as cervical spine fractures, multiple limb fractures, closed head injury, internal organ injuries are typically associated with high-velocity mechanisms and potential spinal instability.

In summary, DANTE is designed only as a guideline and teaching tool for physicians to increase clinical suspicion of potential early and late mechanical and neurological spinal instability.

Keywords: Spinal Instability, Thoracolumbar Trauma, Thoracolumbar Fracture

A2-13

INCREASES IN INFLAMMATION-ASSOCIATED MIRNAS AND CHARACTERIZATION OF LONG-TERM OUTCOMES IN A CCI MODEL OF TBI

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Traumatic brain injury causes life-long changes in the brain that can lead to neuropsychiatric symptoms, cognitive deficits, metabolic dysfunction, and dementia, but how molecular events contribute to long-term dysfunction is largely unknown. The controlled cortical impact (CCI) mouse model of traumatic brain injury is a useful tool for examining the molecular cascades following TBI. One important class of regulatory molecules in the brain, responsible for CNS development, function, and disease are miRNAs. We have identified 3 inflammation-associated miRNAs with increased expression following TBI. Although these miRNAs are involved in immune cell development, we found that they were highly expressed in neurons of both the injured cortex and hippocampus. Genetic knock-out mice are being used to determine the role that these miRNAs may have in neuronal survival and function after TBI.

Although there are many approaches to characterizing the acute damage after CCI, the long-term phenotype of this model is still lacking. To address this deficit, we have characterized the phenotype of mice after mild (0.5 mm), and moderate (1.0 mm) CCI compared to craniotomy only as well as naïve mice controls using a multifactorial approach. Activity and feeding were monitored continuously for 21 days using a home cage system, allowing for non-biased collection of behavioral data. In addition, oxygen consumption rate was measured as an indicator of metabolic changes. To examine neuropsychological alterations, tail suspension, open field, and elevated zero maze texts were performed. Using this approach we have identified quantitative methods for measuring long-term deficits following CCI. These data will inform our characterization of knock-out mice and allow us to link acute molecular changes with meaningful outcomes.

Keywords: inflammation, microRNAs, animal models, molecular mechanisms

A2-14

ENHANCING HIPPOCAMPAL NEURON SURVIVAL AFTER MULTIPLE BRAIN INJURIES BY HUMAN NEURAL STEM CELL-SECRETED GLIAL CELL LINE-DERIVED NEU

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Peoples with traumatic brain injury (TBI) often suffer from bleeding and hypotension. We hypothesize that neural stem cell grafting will attenuate cognitive impairments in TBI plus hemorrhagic ischemia, which is mediated by NSC-secreted glial cell-derived neurotrophic factor (GDNF) to protect host hippocampal neurons from secondary damage. A rat fluid percussion injury (FPI) followed by induced hemorrhagic shock is applied in this study. Rats received a 2.0-atm parasagittal FPI, followed 40-min later by withdrawing blood from the right common jugular vein to lower the mean arterial pressure to 40 mmHg. One day after injury, animals received either vehicle injection or hNSC transplantation near the injured hippocampus. To determine the role of GDNF, GDNF neutralizing or IgG control antibody was given through Alzet pumps immediately after cell transplantation. Morris water maze (MWM) tests were performed on all animals starting on days 7 or 28 post injury, followed by brain tissue collection. Rats with hNSC transplantation showed improved spatial learning and memory at a later time point. Histological analyses of rat brains indicated that hNSC transplantation improved hippocampal neuron

survival by preserving more NeuN positive cells than in control rats. Such neuroprotective effects were blocked by co-treatment with GDNF neutralizing antibody. Western blot analyses revealed that rat brains with hNSC transplantation expressed higher levels of GDNF receptors, as well as phosphorylated ERK, AKT and GSK3β-S9. In summary, our results demonstrate that hNSC grafts have a beneficial effect on neuronal survival in rat hippocampi after TBI plus hemorrhage, and the underlying mechanism of this neuronal protection is at least partially due to GDNF-mediated modulation of the key survival signaling pathways.

Keywords: traumatic brain injury, GDNF, neural stem cell, hippocampus, signal pathway

A2-15

ACUTE EFFECTS OF 17ß-ESTRADIOL ON OXIDATIVE STRESS RESPONSE PROTEINS AFTER TBI

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Background: Traumatic brain injury (TBI) induces secondary cellular damage mediated in part by reactive oxygen species that initiate oxidative stress responses in neuronal and cerebrovascular tissue. The expression of oxidative stress response genes is altered in both hippocampus and cerebrovasculature by TBI and is partially restored by acute treatment with 17β-estradiol (E_2). Additionally, TBI alters the expression of cerebrovascular gap junction proteins (connexins). Here we investigate the effect of E_2 treatment after TBI on connexin proteins and selected protein products of oxidative stress response genes.

Methods: Ovariectomized female rats received moderate fluid-percussion or sham injury followed 15 min later by vehicle (Veh, 1 ml/kg, s.c.) or E_2 (33 μg/kg, s.c.), providing three treatment groups (Sham + Veh, TBI + Veh, or TBI + E_2). Brains were harvested 15 min after treatment and fresh frozen. Cerebral blood vessels were isolated and total proteins extracted. Western blot analysis was performed using antibodies against uncoupling protein 3 (UCP3), glutathione peroxidase 2 (GPX2), and connexin 43 (Cx43).

Results: One-way ANOVA followed by Tukey's HSD test showed an overall effect of treatment on UCP3 protein ($F_{(2,8)} = 21.191$, $P = 0.002$) with significant differences between all three treatment groups. TBI significantly reduced UCP3 protein level ($P = 0.002$). E_2 treatment increased UCP3 protein level ($P = 0.042$) but not to the same level as the Sham + Veh group ($P = 0.038$). There were no significant differences in GPX2 and Cx43 protein levels.

Conclusions: Uncoupling proteins are mitochondrial inner membrane anion carriers involved in the electrochemical gradient across the mitochondrial membrane and mitochondrial production of reactive oxygen species. Since estrogens are known to regulate mitochondrial proteins; our data suggest that UCP3 may be a mediator of the protective effects of E_2 on cerebral blood vessels after TBI.

Support: These studies were completed as part of an interdisciplinary research team funded by The Moody Project for Translational Traumatic Brain Injury.

Keywords: estrogen, oxidative stress response, traumatic brain injury, cerebral vasculature

A2-16

CHARACTERIZATION OF BRAIN MATERIAL PROPERTIES FOLLOWING BRAIN BLAST INJURY

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Improvised explosive devices (IEDs) have caused traumatic brain injury (TBI) in approximately 360,000 soldiers over the past decade, many of whom suffer from long-term neurological consequences when treatment is delayed. A better understanding of the mechanical response of the brain during and after these events may assist diagnosis and outcome of bTBI in both clinical and battlefield scenarios. Diagnostic methods using non-invasive stiffness techniques, such as field-deployable ultrasound, rely on detecting changes to the mechanical properties of brain tissue after injury; however, these tools require *a priori* information on mechanical changes to injured tissue. Moreover, changes to the brain mechanical properties with a blast injury may be a) region-specific, b) time-specific, and c) blast severity-specific. The goal of this study is to characterize changes in the mechanical response of brain tissue following blast injury. Thirty adult, male Sprague-Dawley rats were exposed to a primary blast wave at one of two levels of blast severity: low (18–20 psi peak overpressure) or high (30–25 psi peak overpressure). Sham animals that were anesthetized but not blasted were used as a control. Animals were sacrificed at either 2 or 24 hours following injury, whole brains were extracted, and mechanical indentation tests were used to characterize stiffness at five locations: frontal cortex, midbrain superior, midbrain aqueduct, midbrain inferior, and brainstem. Significantly higher forces were measured in the midbrain inferior region in the blast high 24 hour when compared to sham group (+50%, $p < 0.05$). In addition, we observed lower forces in the brainstem region (-43%, $p < 0.05$) of the blast low 24 hour as compared to the sham group. There were no significant changes in the 2 hour groups. The results show a temporal, regionally dependent mechanical response—stiffening in the blast high 24 hour, softening in blast low 24 hour—to injury. The mechanical changes can serve as correlates to injury to improve detection and diagnosis of bTBI.

Keywords: Blast TBI

A2-17

SPINAL CORD INJURY CAUSES DISTINCT ACUTE AND CHRONIC PHASES IN THE TESTES AND BLOOD TESTES BARRIER OF A SPRAGUE-DAWLEY RAT MODEL

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Spinal Cord Injury (SCI) has been shown to reduce fertility in human and rodent males. We have previously shown that SCI causes a sustained breakdown of the blood testis barrier. Increased inflammatory and oxidative conditions in this setting could lead to an immunological infertility due to exposure to the fragile and antigenic cells in the seminiferous tubules. RNA and metabolomics data from these animals support this hypothesis. We have given Sprague-Dawley rats a thoracic contusion SCI, with cohorts in both acute and chronic time points. Acutely, we see time dependent increases in inflammatory and oxidative markers and a massive decrease in transcription of testosterone producing enzymes followed by a decrease in cell cycle regulators, indicating that sperm production is highly disrupted only after the initial fallout of the injury is fully realized. Chronically, we see maintenance of a low level of immune activity and a new steady state different from both naïve and sham

animals. As further evidence of this immune activation, we see increased numbers of neutrophils in acutely injured animals, while the chronically injured animals show an increased number of T cells. This data indicates that SCI causes acute and chronic phases of injury in the testes, much like in the spinal cord itself. This research is the first step in identifying a target for treatment designed to improve or sustain BTB function after SCI in order to enhance fertility; one of our most fundamental biological functions.

Keywords: Blood Testes Barrier

A2-18

DELAYED HYPOXIA FOLLOWING TRAUMATIC BRAIN INJURY EXACERBATES AXONAL INJURY

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Hypoxia immediately following traumatic brain injury (TBI) has been observed to exacerbate injury. In a retrospective cohort of 32 children admitted with TBI to an ICU, delayed hypoxemia ($paO_2 <$ 60 mm Hg) was observed in 10/32 patients with 70% of the episodes occurring in the first 48 hours after admission. It remains unclear whether hypoxia beyond the immediate post injury period influences axonal injury.

Five-week-old male mice (C57BL/6J), underwent controlled cortical impact (CCI) followed by arterial catheterization on post-injury day 1 with arterial blood gas sampling after 30 minutes of hypoxia (8% FiO_2 and 4% CO_2) as well as an assessment of tissue hypoxia utilizing Hypoxyprobe. Twenty mice were subjected to either CCI ($N = 12$) or sham surgery (SHAM) ($N = 8$). One day later awake animals were randomized to 30 minutes of hypoxia or normoxia. White matter axonal injury was quantified 48 hrs post injury utilizing blinded stereological methods on beta amyloid precursor protein (B-APP) and NF-200 stained sections.

Twenty-four hours after CCI, 30 minutes of hypoxia in awake spontaneously breathing mice revealed hypoxemia with normocarbia (paO_2 50.1 ± 1.9 mm Hg and $paCO_2$ 40.7 ± 2.0 mm Hg). Hypoxyprobe immunohistochemistry demonstrated increased gray matter hypoxia in SHAM + hypoxia and CCI + hypoxia compared with SHAM and CCI respectively. However, pericontusional white matter hypoxia was only observed in CCI + hypoxia. In the pericontusional corpus callosum and external capsule there were increased axonal swellings in CCI + hypoxia compared with CCI animals for both B-APP (37 ± 6 vs. 21 ± 6 10^3 axons/mm^3, $P < 0.01$) and NF-200 (34 ± 4 vs. 24 ± 3 10^3 axons/mm^3, $P < 0.01$). Minimal B-APP and NF-200 staining was observed in SHAM and SHAM + hypoxia mice.

A clinically relevant model of delayed hypoxia following TBI resulted in increased pericontusional axonal injury.

Keywords: hypoxia, axonal injury, traumatic brain injury, secondary injury, pediatric

A3 Poster Session I - Group A: Blood-Brain Barrier

A3-01

EVALUATING THE POTENTIAL FOR NANOPARTICLE DELIVERY AFTER TRAUMATIC BRAIN INJURY

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An estimated 1.7 million traumatic brain injuries (TBI) occur annually and account for over 50,000 deaths in the U.S. TBI is initiated by a mechanical insult that leads to a host of cellular and molecular alterations, including transient blood-brain-barrier (BBB) breakdown. Nanoparticles (NP) have played an important role as diagnostic and therapeutic (theranostic) agents in various diseases, but, limited permeability across BBB is a major obstacle for NP-based approaches for neural disease/injury. Thus, the short-lived BBB permeability post-injury may be effectively utilized to deliver NP-based theranostics for TBI. Previous studies with pre-clinical TBI models demonstrated peak permeability of small molecules (~5 nm) at 4–6h post-injury. Yet, there is a critical gap in understanding the behavior of larger particle delivery (>5 nm) after TBI. Therefore, the objective of this study was to investigate the effect of NP's size on extravasation after TBI. Specifically, carboxylated polystyrene NPs of 20, 40, 100, and 500 nm with unique fluorescent spectra were pegylated to both increase circulation time and neutralize the surface charge of the nanoparticles. Pegylated-NP cocktails were then intravenously injected in to mice ($n = 6$ retro-orbital injection) 5h post-injury (controlled cortical impact) and allowed to circulate for 1h prior to sacrifice and perfusion. The brains were frozen, sectioned, and imaged with fluorescent microscopy. Pegylation of NPs led to modest increase in hydrodynamic diameter (~5–7 nm above baseline diameter) and reduced zeta-potential (range: –9 mV to –29 mV). Histological analysis demonstrated the presence of all pegylated-NPs exclusively within the injury penumbra, indicating BBB breakdown and extravasation at 5–6h post-injury. The presence of pegylated-NPs was significantly higher in injured animals compared to control sham animals. In conclusion, we have demonstrated the potential for NP extravasation acutely post-TBI. Further time course characterization will provide insights as to the full utility of NP-based theranostics agents for TBI.

Keywords: Nanoparticles, extravasation, theranostics, systemic delivery

A3-02

ISG15 INTERACTS WITH JUNCTIONAL PROTEINS PRIOR TO BBB DISRUPTION FOLLOWING TBI IN YOUNG MICE

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Introduction: Recently we have shown that ISG15, an ubiquitin like protein is upregulated prior to breakdown of the BBB following TBI and colocalizes with MLCK, which plays a pivotal role in development of cerebral edema. Here we show that ISG15 interactions with junctional protein Claudin 5, and occurs prior to the disruption of the BBB following TBI in young mice. ISG15 is increased following focal ischemia and is neuroprotective. The significance of ISG15 following TBI is still unclear.

Methods: PND21 and PND24 mice were anesthetized with avertin, mechanically ventilated, physiologically regulated, and subjected to lateral closed-skull injury model with impact depth of 2 or 2.25 mm (bregma level - 0.10 mm). Mice were sacrificed at T0, T30m, T4h. ISG15 and MLCK analyzed by western blot, immunohistochemistry; BBB disruption with Fluorescein sodium salt and 4 Kda Dextran.

Results: *Protein expression*

ISG15 down-regulation: PND21 normalized to actin T0 Sham: 14.83 2.00 mm:9.83, 2.25 mm: 3.83 and T4h Sham: 4.5 2.00 mm: 5.5, 2.25 mm: 6.5.

ISG15 up-regulation: PND24 T0 Sham: 5.167, 2.00 mm: 9.167, 2.25 mm: 14.17 and T4 Sham: 4.5, 2.00 mm: 9.5, 2.25 mm: 14.

ISG15 and Claudin develop protein-protein interactions on co-immunoprecipitation increased in TBI compared to shams.

Blood Brain Barrier Disruption

Fluorescein and Dextran ng/grams of brain: Fluorescein- PND21 T0 Sham: 2, 2.00 mm: 3.5, 2.25 mm: 4.25. T4h T0 Sham: 2.25, 2.00 mm: 6.33, 2.25 mm: 13. PND24 T0 Sham: 2.25, 2.00 mm: 3, 2.25 mm 4. T4h Sham: 2, 2.00 mm 5.33, 2.25 mm 9.33.

Dextran-PND21 T0 Sham: 6.8, 2.00 mm 8.6 2.25 mm: 9.3. T4h Sham: 10 2.00 mm: 20, 2.25 mm: 40. PND24 T0 Sham: 2.25, 2.00 mm: 3.25, 2.25 mm: 3.25. T4h Sham: 2, 2.00 mm: 5, 2.25 mm: 10.5. 13.223, 4h 2.00 mm: 9.333, 2.25 mm: 15.50

Conclusion: Delay in upregulation of ISG15 in PND21 mice compared to PND24 mice may play a role in worse outcomes in younger children following TBI.

Keywords: pediatrics, mouse model, development, proteins

A3-03

ENDOTHELIAL TARGETED ANTIOXIDANT ENZYME THERAPY TO COMBAT SECONDARY INJURY AND PRESERVE BBB INTEGRITY FOLLOWING EXPERIMENTAL TBI

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An estimated 1.7 million traumatic brain injuries (TBI) occur each year, and TBI is a contributing factor to one third of all injury related deaths in the United States alone. Current treatment for TBI is supportive, and the pathophysiology is not fully understood; however, evidence suggests high-energy oxidants and oxidative stress as mediators of secondary damage in TBI, including blood brain barrier (BBB) hyperpermeability. A novel endothelial targeted antioxidant enzyme approach to TBI therapy is hypothesized to quench reactive oxygen species (ROS) at their source to protect BBB function. While constitutively expressed molecules can be targeted for prophylactic and therapeutic drug delivery, determinants expressed or upregulated in pathological states are ideal for localized therapeutic intervention. Here, we propose a strategy that targets the activated endothelium following TBI. Conjugates of anti-PECAM-1 and anti-ICAM-1 antibodies to catalase were prepared through amino chemistry for administration to C57BL/6 mice after controlled cortical impact (CCI) model of moderate TBI (impact parameters: 3.5 m/s, 2 mm tip, 1 mm depth, 0.5 s dwell time). Previously, the anti-PECAM-1/catalase conjugate was found to alleviate vascular oxidative stress in lung ischemia/reperfusion injury. The use of antibody/antioxidant enzyme conjugates has not been investigated in the context of TBI. Preliminary data from isolated cerebral microvasculature suggests an increase in expression of cell adhesion molecules, PECAM-1 and ICAM-1, after TBI. Furthermore, we have demonstrated increased in situ dihydroethidium (DHE) fluorescence detection of ROS in the brain, thus supporting the proposed therapy as a potential means to ameliorate secondary mechanisms of injury and to maintain BBB homeostasis in neurotrauma.

Keywords: Antioxidant enzymes, Traumatic brain injury, Controlled cortical impact, Endothelial biology

A3-04

PROFILE OF BLOOD BRAIN BARRIER DISRUPTION FOLLOWING SINGLE AND REPEATED CLOSED HEAD IMPACT CONCUSSION IN RATS

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Blood brain barrier (BBB) disruption is a pathologic hallmark of severe traumatic brain injury (TBI) that is associated with neuroinflammatory events contributing to cell death and edema. However, the extent to which the BBB may be compromised following concussion or mild TBI (mTBI) are not well understood. In the current study the WRAIR projectile concussive impact (PCI) injury model was used to assess the effect of concussion on the expression of BBB proteins. Rats were anesthetized, fitted with a helmet designed to prevent skull fracture and a projectile was launched at their head to induce a closed-head concussive impact injury resulting in mTBI. Groups consisted of animals exposed to sham surgery (anesthesia only), a single concussion and multiple concussions (4 impacts spaced 1 hour apart). Animals were sacrificed at 6h, 24h, or 72h post-injury. Immunohistochemistry was performed to quantify the expression of proteins associated with the BBB structure/functions including claudin-5 (CL5), zona occulden-1 (ZO1), and aquaporin-4 (AQ4). Positive-stained areas were quantified in the parietal cerebral cortex. Significant reductions in CL5 expression were detected at 72h post-injury following a single concussion ($p < 0.05$ vs. sham). However, repeated concussion produced significant decrements in CL5 expression that were apparent at 6h post-injury and sustained out to 72h post-injury ($p < 0.05$ vs. sham). Likewise, significant reductions in Z01 protein expression were detected at 72h post-injury, but only in animals that received multiple concussions ($p < 0.05$ vs. sham). No significant effects were detected in AQ4 expression at any post-injury time point following single or repeated concussion.

Overall, these results indicate initial evidence of BBB disruption following a single concussion that is worsened following multiple concussions in the PCI model. Notably, the pattern of delayed degradation of CL5 and Z01 protein expression following single concussion or repeated concussion suggests a progressive gradient in BBB disruption that is likely mediated by secondary causes, such as neuroinflammation and oxidative stress.

Keywords: Concussion, mTBI

A4 Poster Session I - Group A: Pediatric

A4-01

PHASE I TRIAL OF N-ACETYLCYSTEINE IN COMBINATION WITH PROBENECID IN CHILDREN AFTER SEVERE TRAUMATIC BRAIN INJURY

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N-acetylcysteine (NAC) is being evaluated in clinical trials targeting multiple neurological diseases including TBI; yet existing data suggest it has limited if any penetration into normal brain. NAC serves as a cysteine donor for synthesis of the prominent intracellular

antioxidant glutathione (GSH). Probenecid can maintain intracellular GSH stores and potentially increase brain exposure to NAC via inhibition of drug transporters. We sought to determine whether the combination resulted in detectable CSF drug concentrations and in any adverse events.

IRB approved, randomized, double-blind, placebo controlled Phase I study in children (2–18 y) after severe TBI (GCS ≤ 8). Inclusion criteria: externalized ventricular drain and indwelling vascular catheters to obtain CSF and blood, respectively. After informed consent patients were randomized to receive probenecid (25 mg/kg load then 10 mg/kg/dose q6h × 11) and NAC (140 mg/kg load then 70mg/kg/dose q4h × 17), or placebo of equal volume and timing. Serum and CSF samples were drawn pre-bolus and at 1, 24, 48, 72, and 96h after randomization and drug concentrations were measured (HPLC-MS/MS).

Fourteen patients were enrolled (7/group). Age, initial GCS, gender, and race weren't different between groups. In the drug treated group serum NAC concentrations ranged from 19.8 ± 13.7 to 16.8 ± 8.7 μg/ml and CSF NAC concentrations ranged from 214.6 ± 239.0 to 467.9 ± 695.0 ng/ml (1 to 96h post-bolus; mean ± SEM). There were no adverse events attributable to drug treatment. Temperature, blood pressure, intracranial pressure (ICP), and the use of ICP-directed therapies were not different between groups.

Treatment with NAC and probenecid resulted in detectable concentrations of NAC in CSF and was not associated with undesirable effects after TBI in children. Our data coupled with other clinical studies support larger trials evaluating pharmacokinetics and outcome with combination therapy, in addition to evaluating NAC alone.

Support: R01NS069247

Keywords: Phase I Clinical Trial, N-acetylcysteine, Probenecid, Drug Transporters

A4-02

FATTY ACID OXIDATION IS INCREASED SELECTIVELY IN ASTROCYTES OF INJURED HIPPOCAMPUS AFTER TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) is the leading cause of permanent lifelong disability in children and is characterized by deficits in cognition, attention and sensory-motor integration. Impaired oxidative glucose metabolism following TBI further contributes to cell death. The role of fatty acid (FA) oxidation after TBI, however, is unknown. The developing brain utilizes fatty acids for energy and metabolism, while the adult brain only uses FA under pathologic conditions. Mitochondrial β-oxidation of fatty acids supports energy production and metabolic homeostasis, especially during the periods of fasting and stress. To be oxidized in mitochondria, fatty acids must be converted to acyl-carnitine esters by transfer of acyl groups to l-carnitine. This reaction is catalyzed by Carnitine Palmitoyl Transferases (CPT1a and CPT2), which are located on the outer and inner mitochondrial membranes respectively. Only then are acyl-carnitines transported into mitochondria to support oxidative metabolism. This study is the first to examine fatty acid oxidation after TBI.

Postnatal day 21–22 male rats were anesthetized with isoflurane and TBI was administered using a controlled cortical impact to the left parietal cortex. Fatty acid oxidation in the cortex and hippocampus was measured using [1-14C] oleic acid, and oxidation was increased after TBI in the ipsilateral hippocampus but not in the cortex. The concentration of carnitines in both the cortex and hippocampus was unchanged after TBI. Using immunofluorescence, we determined that astrocytes are the only cells expressing CPT1a and CPT2, thus the only cells able to use fatty acids for energy and metabolism. There were no significant differences in the amount of CPT1a and CPT2, quantified via western blotting, at 6 and 24 hrs after TBI. This study provides strong evidence that astrocytes selectively utilize fatty acids for energy and metabolism and this early astrocytic support leads to improved recovery after TBI in the developing brain.

Keywords: Metabolism

A4-03

20-HETE INHIBITION IMPROVES OUTCOME IN A PEDIATRIC RAT MODEL OF TRAUMATIC BRAIN INJURY

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Previous work has shown that inhibition of 20-hydroxyeicosatetraenoic acid (20-HETE) formation by cytochrome P450 (CYP) omega-hydoxylation of arachidonic acid can protect immature and mature brain from ischemia. We tested the hypothesis that post-treatment with the 20-HETE synthesis inhibitor N-hydroxy-N-4-butyl-2-methylphenylformamidine (HET0016) can protect the immature brain from traumatic brain injury (TBI). Male Sprague Dawley rats (postnatal day 9–10) were subjected to controlled cortical impact (CCI; 3 mm impactor; velocity 5.5 m/s; depth 1.5 mm), and studied in 3 groups: 1) sham-operated, 2) vehicle-treated TBI, and 3) HET0016-treated TBI (1 mg/kg, ip, at 5 min and 3 h post-injury). Lesion volume and microglia morphology (Neurolucida) were measured. Expression of inflammatory factors (Real-time PCR of TNFalpha, IL-1beta, IL-4, IL-10), microglia activation (CD68/Iba-1), neuron loss (NeuN/DAPI), and astrocyte activation (GFAP) were evaluated. Neurologic testing (foot fault, novel object recognition) was performed at 30 and 90 days. Lesion volumes in the vehicle-treated TBI group were 12.9 ± 1.9, 15.4 ± 4.9 and 18.2 ± 0.8% of hemisphere at 3, 7 and 30 days. HET0016-treated TBI groups had significantly reduced lesion volumes (6.2 ± 1.9, 5.5 ± 1.3 and 8.8 ± 0.9%). HET0016 treatment significantly increased number and length of processes of microglia (3d, 30d), and significantly decreased microglia cell body area (7d, 30). Peri-lesion gene expression of pro-inflammatory cytokines (TNFalpha, IL-1beta) was lower at 1d, and reparative cytokines (IL-4, IL-10) expression was higher at 3d with HET0016-treatment. HET0016 decreased the number of CD68-positive microglia in peri-lesion cortex, neuronal loss in ipsilateral thalamus, and GFAP intensity of astrocyte staining around the contralateral hippocampus and cortex. Contralateral hind limb foot faults were reduced, and discrimination index for exploring a novel object was improved at 30 days post-injury with HET0016. In conclusion, HET0016 reduced lesion volume and improved neurologic outcome after TBI in immature rats. The potential protective mechanism may be related to 20-HETE-induced pro-inflammatory state of microglia, as evident by HET0016 attenuation of pro-inflammatory cytokines, later augmentation of reparative cytokines, and an accelerated recovery of microglia to a ramified state.

Keywords: 20-hydroxyeicosatetraenoic acid, arachidonic acid, microglia

A4-04

LARGE-ANIMAL COMBINED INSULT MODEL FOR INFLICTED BRAIN INJURY IN INFANCY

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Research elucidating the pathophysiology of non-accidental trauma in infants and young children has been limited by the lack of appropriate translational models. While widespread, diffuse bilateral brain damage can be created readily by a number of global insults, infants with subdural hematoma may have extensive unilateral damage (''hemispheric hypodensity'') with sparing of the opposite hemisphere. Here we describe tissue damage in our model of abusive head trauma. Piglets age 7–30 days (n = 18) were anesthetized and underwent cortical impact, mass effect via epidural balloon inflation, unilateral subdural hemorrhage, and multiple rounds of apnea, hypoventilation, and seizures induced with intravenous bicuculline or a sham surgery was performed (n = 5). After injury, piglets survived under anesthesia for up to 24 hours, with some subjects undergoing CT or 3T MRI. Brains were examined for neuronal death. Injection of subdural blood after mechanical brain deformation enabled placement of a large but thin unilateral hematoma, similar to those seen in human children, in 90% of subjects, likely due to traumatic separation of the dural border cells. Seizures lasted 20.25 ± 6.2 minutes and were accompanied by tachycardia, elevated mean arterial pressure, and decreased oxygen saturation. During apnea and hypoventilation, subjects developed transient hypotension, bradycardia, and hypoxia, followed by persistent alterations in mean arterial pressure and reduced arterial pH. Asymmetric edema in the affected hemisphere was demonstrated in a subset of subjects via imaging and/or necropsy. To date, the density of damaged neurons in the CA4 region of the hippocampus may be greater ipsilateral vs. contralateral to the subdural hematoma. This is the first immature large-animal model using the combined physiologic insults experienced by children with severe inflicted traumatic brain injury with unilateral subdural hematoma and asymmetric brain damage. Further studies with this model will facilitate exploration of the pathophysiology and possible treatments for this common and highly morbid injury pattern unique to infants and toddlers.

Keywords: Abusive Head Trauma, Seizures, Brain Pathology, Swine

A4-05

MAGNETIC RESONANCE SPECTROSCOPY IMAGING OF THE HIPPOCAMPUS AT 7T AFTER MILD TBI IN IMMATURE BRAIN

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Mild traumatic brain injury (mTBI) in children is a common and serious public health problem. Traditional structural neuroimaging techniques are often normal in children who sustain mTBI putting them at risk for repeated episodes of mTBI (rmTBI). There is a need for non-invasive and more sophisticated imaging techniques capable of detecting changes in neurophysiology after injury. In this study we examined metabolite changes in immature brain resulting from mTBI and rmTBI using proton magnetic resonance spectroscopy (^{1}H-MRS). Eighteen day old male rats were divided into three groups; Sham (n = 8), mTBI (n = 9, single impact), rmTBI (n = 10-three impacts 24h apart). The hippocampus in each rat was examined at 7 Tesla, 7 days post injury. After mTBI and rmTBI, N-acetylaspartate/creatine ratio (NAA/Cr) was significantly reduced ($p = 0.03$, $p < 0.0001$, respectively), and the myo-inositol/creatine ratio (Ins/Cr) significantly increased ($p = 0.017$, $p = 001$, respectively) compared to sham controls. The choline/creatine (Cho/Cr) and lipid/creatine (Lip/Cr) ratios were significantly decreased ($p = 0.04$, $p = 0.02$, respectively) after rmTBI vs. sham. There was a small, but significant, further reduction ($p = 0.01$) in the NAA/Cr after rmTBI vs. mTBI. NAA/Cho was not significantly different between injured vs. sham rats. We conclude that there is alteration in NAA and Ins after mTBI and rmTBI likely reflecting neuroaxonal cell damage and glial proliferation, respectively. The decrease in Cho and Lip after rmTBI may reflect damage to axonal membrane and parallels the axonal argyrophilia observed in hippocampal region with silver staining at d7 after injury. These findings may be relevant to understanding the extent of disability following mTBI in the immature brain.

Support: NS061817, NS076511.
Keywords: MRS

A4-06

CHRONIC WHITE MATTER DAMAGE FOLLOWING PEDIATRIC TRAUMATIC BRAIN INJURY

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Objective: Differences in white matter integrity in children and adolescents with traumatic brain injury (TBI) in the post-acute and chronic stage was investigated; hypothesizing that children with TBI would demonstrate significantly lower fractional anisotropy (FA), compared to extracranial injury (EI) and typically developing (TD) groups in the corpus callosum and frontal and temporal lobes.

Methods: Diffusion tensor imaging was utilized to examine between-group differences in white matter integrity 6-weeks and 12-months post-injury in children and adolescents aged 8–15 with TBI ($n = 10$; 3 mild, 2 moderate, 5 severe; $M = 12.4$ yr; SD = 2.2), EI ($n = 10$; $M = 12.7$ yr; SD = 2.8), and a TD group ($n = 11$; $M = 12.0$ yr; SD = 2.4). Groups did not differ significantly by IQ or age.

Data were acquired on a Philips 3T MR scanner. Scans were manually checked for motion. The standard FSL pipeline was used for Tract-Based Spatial Statistics analysis. Statistical comparisons using the FSL RANDOMISE function were used to generate two-sample T-tests comparing FA between groups controlling for age.

Results: 6-weeks post-injury, results demonstrated lower FA in the TBI group than the TD group throughout frontal, temporal, and parietal regions, primarily in the corpus callosum, longitudinal fasciculi, cerebellum and cingulum ($p < .05$). Additionally, FA remained significantly lower in the TBI group at 12-months, specifically in the anterior corona radiata, cingulum, superior longitudinal fasciculus, and corpus callosum ($p < .05$).

When comparing TBI and EI groups, FA was significantly lower in the TBI group at 6-weeks, specifically in the fronto-occipital fasciculi, genu of the corpus callosum, left superior longitudinal fasciculus, and cingulum ($p < .05$). However, there were no significant differences between TBI and EI groups at 12-months. No differences in FA were evident between TD and EI groups.

Conclusion: Following pediatric TBI, white matter integrity damage is evident at 6-weeks and remains 1-year post-injury. Findings indicate long-lasting effects of TBI in the cingulum, superior longitudinal fasciculi, and corpus callosum with some recovery between the acute and chronic stages.

Keywords: Diffusion Tensor Imaging, White Matter Integrity, Pediatrics

A4-07

AVAILABILITY OF OUTPATIENT REHABILITATION SERVICES AND BARRIERS TO CARE FOR VULNERABLE POPULATIONS AFTER PEDIATRIC TBI

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Objective: Aims were to explore associations between English proficiency, insurance status and outpatient rehabilitation service availability and travel time for children with traumatic brain injury (TBI).

Design: This study used an ecologic cross-sectional design. Data were analyzed from a cohort of 82 children (<18 years) treated for moderate to severe TBI and rehabilitation providers in Washington State. Main measures included availability and travel time to rehabilitation services.

Results: Fewer than 20% of rehabilitation providers accepted children with Medicaid and provided language interpretation services. Mental health service provision was most limited. Adjusted for median household income, availability of multilingual services was lowest in counties with greater language diversity; for every 10% increase in persons over 5 years old speaking a language other than English at home, there was a 34% decrease in availability of multilingual pediatric services (Prevalence ratio = 0.66; 95%; CI: 0.48–0.90). Adjusted for education and Medicaid status, children from Spanish-speaking families with limited English proficiency had significantly longer travel times to all services: mean of 16 additional minutes to mental health and 9 additional minutes to other therapies.

Conclusions: Children in households with limited English proficiency and Medicaid insurance faced significant barriers in availability and proximity of outpatient rehabilitation services. There is a need for innovative service strategies to equitably improve availability of services for children with TBI. Studies in other regions utilizing similar methods are needed to understand the scope of disparities noted in this study.

Keywords: TBI, rehabilitation, healthcare disparities, healthcare accessibility, disability

A5 Poster Session II - Group A: Biomarker

A5-01

SINGLE MOLECULAR ARRAY GLIAL FIBRILLARY ACID PROTEIN AND TOTAL TAU ARE INCREASED UP TO 90 DAYS AFTER TRAUMATIC BRAIN INJURY

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Background: Glial fibrillary acid protein (GFAP) and tau are promising diagnostic and prognostic biomarkers in traumatic brain injury (TBI). Single Molecule Array (Simoa) is a novel technology which employs highly sensitive immunoassays for accurate measurements of candidate biomarkers.

Design/Methods: Plasma tau and GFAP were measured by Simoa in serial samples from 33 TBI subjects (mean age 37; 73% male) at days 1, 30 and 90 after TBI and compared to those of uninjured controls (n = 70).

Results: GFAP was increased at days 1 (16.75 (3.84–100.6) pg/ml, 30 (1.330 (0.742–2.080)) pg/ml and 90 (1.350 (0.8870–2.280) pg/ml after TBI compared to controls (0.5280 (0.216–1.220) pg/ml, ($p < 0.0001$ for all comparisons). Tau was similarly increased at days 1 (9.560 (5.895–17.10) pg/ml, 30 (6.665 (4.705–9.163) pg/ml, and 90 (5.720 (3.850–7.180) pg/ml compared to controls (4.340 (2.745–5.128) ($p < 0.0001$, $p < 0.0001$ and $p = 0.0044$, respectively). Receiver-operator characteristic analysis found that the area under curve (AUC) for tau at days 1 and 30 was 0.8973 (95% CI 0.8238 to 0.9709), and 0.8172 (95% CI 0.7254 to 0.9090) respectively. AUC for GFAP at day 1 was 0.9655 (95% CI 0.9212 – 1.010). There was a moderate correlation ($r = 0.5256$ (95% CI 0.1704 to 0.7600, $p = 0.0049$) between total tau and GFAP at day 1 after TBI and an inverse correlation between day 1 GFAP and Glasgow Outcome Scale Extended-rated recovery at day 180 ($r = -0.4469$ (95% CI –0.7316 to - 0.02953, $p = 0.0325$).

Conclusions: Tau and GFAP are increased up to 90 days after TBI. Tau and GFAP measured by Simoa may be useful as biomarkers of TBI in the both acute and subacute phases.

Keywords: highly sensitive immunoassays, glial fibrillary acid protein, total tau, diagnostic and prognostic biomarkers

A5-02

PERIPHERAL BLOOD MITOCHONDRIAL DNA AS A BIOMARKER OF CEREBRAL MITOCHONDRIAL DYSFUNCTION FOLLOWING TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) has been shown to activate the peripheral innate immune system and systemic inflammatory response, possibly through the central release of damage associated molecular patterns (DAMPs). We hypothesized TBI would increase peripheral whole blood relative mtDNA copy number, and would be associated with alterations in cerebral mitochondrial bioenergetics triggered by TBI. Blood samples were obtained before, 6, and 25 hrs after focal (controlled cortical impact injury: CCI) and diffuse (rapid non-impact rotational injury: RNR) TBI. PCR primers, unique to mtDNA, were identified by aligning segments of nuclear DNA (nDNA) to mtDNA, normalizing values to nuclear 16S rRNA, for a relative mtDNA copy number. Three unique mtDNA regions were selected, and PCR primers where designed within those regions, limited to 25–30 base pairs to ensure sequence specificity, and measured utilizing qRT-PCR. Mean relative mtDNA copy numbers increased significantly following both CCI and RNR. Specifically, the mean relative mtDNA copy number from three mitochondrial specific regions pre-injury was 0.84 ± 0.05. After diffuse non-impact TBI at 6 and 25 hours, mean mtDNA copy

number was significantly higher, 2.07±0.19 (P<0.0001) and 2.37±0.42 (P<0.001), respectively. Following focal impact TBI, relative mtDNA copy number was also significantly higher, 1.35±0.12 (P<0.0001) at 25 hours. Alterations in mitochondrial respiration in the hippocampus and cortex performed post-TBI correlated with changes in peripheral blood relative mtDNA copy number. Our data suggests that isolated TBI stimulates the peripheral innate immune response, likely stimulating mitochondrial biogenesis of leukocytes and circulating free-extracellular mtDNA. In addition, alterations in peripheral blood relative mtDNA copy numbers may be a novel biosignature of cerebral mitochondrial bioenergetics with exciting translational potential for non-invasive diagnostic and interventional studies.

Keywords: Pediatric traumatic brain injury, Mitochondria, mitochondrial DNA, Biomarker, Cerebral Bioenergetics, Blood

A5-03

ALTERATIONS OF CIRCULATING CHEMOKINES IN RELATION TO NEUROLOGICAL OUTCOME AFTER MODERATE-TO-SEVERE TRAUMATIC BRAIN INJURY

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Background: Migration of peripheral inflammatory cells into the central nervous system (CNS) is known to contribute to secondary injury mechanisms after traumatic brain injury (TBI). Cellular activation and infiltration of leukocytes into the brain is orchestrated by changes in the expression of chemokines and their receptors; this process may initiate CNS repair after trauma, but can also exacerbate injury via disruption of the blood-brain barrier and induction of vasogenic edema, with adverse consequences on patient outcome. Thus, evaluation of circulating chemokine profiles early post-injury may further our understanding of their role in TBI, and their relationship to patient outcome.

Purpose: Using a multimarker approach to characterize changes in blood chemokines in the acute period following moderate-to-severe TBI, and in association with 6-month neurological outcome using the extended Glasgow Outcome Scale.

Methods: Peripheral blood was drawn from 181 TBI patients ($N=138$ severe, $N=43$ moderate) on admission, 6-, 12-, 24-h post-injury; matching control samples were collected from healthy volunteers ($N=21$). Plasma concentrations (pg/mL) of eotaxin, eotaxin-3, interferon-inducible protein (IP)-10, interleukin (IL)-8, monocyte chemotactic protein (MCP)-1, –4, macrophage derived chemokine (MDC), macrophage inflammatory protein (MIP)-1β, and thymus-and activation-regulated chemokine (TARC), were quantified using a high-density, ultra-sensitive MULTI-ARRAY® immunoassay.

Results: Significant increases in all chemokines assayed were observed over the 24 h sampling period in patients, with the exception of eotaxin-1, which was not altered, and both MDC and IP-10, which were reduced relative to controls. Elevated admission levels of IL-8, MCP1, MIP-1β and eotaxin-1 were associated with poor 6-month neurological outcome, while altered levels of 7 of 9 assayed chemokines were associated with mortality.

Conclusion: TBI patients display altered systemic chemokine profiles. These alterations are associated with negative patient outcome at 6-months and support potential roles in modulation of neuroinflammation and neuroregeneration after TBI.

Keywords: neuroinflammation, IL-8, MCP1, MIP-1β, eotaxin-1

A5-04

NEURON-SPECIFIC ENOLASE IS SIGNIFICANTLY CORRELATED TO OUTCOME POST TRAUMATIC BRAIN INJURY, ALBEIT NOT IN PRESENCE OF SERUM S100B

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Background: Neuron-specific enolase (NSE) and S100B are biomarkers of different cellular origin that mirror distinct types of injury and pathophysiological mechanisms in TBI. The aim of this study was to determine NSE correlation to cerebral injury and towards outcome in models with, and without, S100B.

Materials and Methods: A total of 340 TBI patients admitted to the neuro-intensive care unit at Karolinska University Hospital, from 2005–2011 were included. Serum S100B and NSE were measured in a first sample obtained within 48h, and in additional two samples obtained within 72h after trauma. Clinical data were acquired from hospital charts. Glasgow outcome score (GOS) was evaluated 3 months after trauma. Regression analyses were performed to examine associations between biomarkers and injury severity and outcome. The pseudo-R^2 (i.e., the percentage variance in outcome explained by the variables) was calculated.

Results: Peak NSE and S100B serum levels were correlated ($r=0.61$, $p<0.0001$). In univariate analyses, NSE levels were not correlated to the cerebral injury on CT scans, while S100B levels was (Stockholm CT-score, $p=0.0014$). Biomarker levels sampled later after trauma yielded more accurate outcome prediction than the initial levels (NSE, 1st sample pseudo-$R^2=0.8\%$ vs. 3rd sample 7.7%; S100B, 1st 4.8% vs. 3rd 17.6%). Models including age, Glasgow coma scale, pupil responsiveness, injury severity score, Stockholm CT-score and S100B presented a pseudo-R^2 of 37.3%, while the same model including NSE, instead of S100B, yielded only 33.3%. NSE did not have an additional contribution when was used in the S100B-model ($p=0.8$).

Conclusion: Serum levels of NSE are correlated to outcome with an increasing predictive capability in later samples. However, NSE did not correlate with injury severity as assessed by CT; neither does it provide any additional information in the presence of S100B.

Keywords: Biomarkers, Traumatic brain injury, Outcome prediction, NSE, S100B

A5-05

TRANSCRANIAL DOPPLER MEASURES EFFECTS OF MIND-BODY TRAINING ON CEREBRAL AUTOREGULATION IN SERVICE MEMBERS WITH COMBAT RELATED TBI

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Background: Disruption of the autonomic nervous system, including cerebral vasoreactivity (CVR), has been observed following acute traumatic brain injury (TBI) and may also be associated with chronic TBI symptoms. In chronic mild TBI (avg 2.3 years), we recently reported that over 40% of service members (SM) exhibited abnormal cerebral vasodilatory response to CO_2 during breath holding index (BHI) using Transcranial Doppler (TCD). To address this

physiological disturbance, we integrated mind-body techniques, known to affect parasympathetic tone and autonomic balance, into a four-week intensive interdisciplinary outpatient treatment program for SM with combat-related TBI and psychological health (PH) conditions. We measured BHI on admission and discharge, hypothesizing that this program will have a beneficial effect on autonomic function.

Methods: TCD with breath holding paradigm was performed on patients admitted to the National Intrepid Center of Excellence. As a part of integrative care, SMs received an average of 8 sessions of mind-body training per week. Thirty-four patients with abnormal BHIs upon admission were tested again at the end of the treatment program.

Results: Over seventy percent (n = 24) of the patients exhibited improved (i.e., increased) BHI scores. A paired-sample t-test showed that BHI scores were significantly higher ($t = -2.81$, $p = .008$, $d = .46$, medium effect size) on the second TCD ($M = 1.16$, $SD = .31$) than the first TCD ($M = 1.02$, $SD = .20$), with 38.2% (n = 13) of patients resolving within the normal range ($BHI \geq 1.2$).

Conclusions: TCD CVR evaluation in patients with chronic mTBI revealed a high prevalence of cerebral autonomic disturbance. Exposure to mind-body training was associated with improved cerebral autoregulation as measured by changes in BHI, suggesting that TCD BHI might have utility as a marker of treatment response in patients with mTBI and PH conditions.

Disclaimer: Any opinions, views, or assertions expressed are solely those of the authors and do not necessarily represent those of NICoE, WRNNMC, CNRM, the Uniformed Services University of the Health Sciences, the Department of Defense, Department of Army/Navy/Air Force, or the U.S. government.

Keywords: sympathetic nervous system, parasympathetic nervous system, traumatic brain injury, transcranial doppler, military service members

A5-06

PROGRESSIVE LIMBIC ANTEROGRADE TRANS-NEURONAL DEGENERATION: A NEUROPATHOLOGICAL & RADIOLOGICAL BIOMARKER IN HIPPOCAMPAL DISEASE

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In 1977 Torch et al. (Neurology, 27: 1157) described the case of a 64-year-old man erroneously diagnosed with Alzheimer's Disease (AD). In the absence of typical AD-pathology, the unexpected autopsy finding of a left hippocampal cystic infarct, with extensive 1^0, 2^0 & 3^0 limbic anterograde trans-neuronal-degeneration (LATND) accounted for a previously noted left-temporal EEG slow wave focus and 8-year history of progressive dementia. Question arose as to whether LATND in this case was: 1) a rare neuropathological event; 2) an unrecognized phenomenon due to the prosector's lack of awareness; or 3) more prevalent than commonly appreciated. As presented in Part I of this two-part presentation, subsequent clinical-neuropathological metaanalysis by this author of over 128 published cases of hippocampal injury, concluded that LATND: 1) commonly occurs in many neurological conditions in both children & adults (e.g., TBI/CTE, stroke, limbic encephalitis and kernicterus, Atypical & Familial AD, carcinomatous vasculitis, etc); 2) occurs uni- and bilaterally, where the extent, degree & rate of progression in each hemisphere is related to ''Survival Time'' [ST-duration of time from symptom-onset to death], including acuity, chronicity, severity of disease; 3) may be accompanied by a progressive two-stage syndrome of cognitive, emotional & behavioral encephalopathy, where, in its first early phase, transsynaptic denervation-hypersensitivity and/or neuronal disinhibition it may be expressed by ''positive'' psychomotor symptomatology, and in later end-stage, by ''negative'' symptomatology, reflecting anterior thalamic/diencephalic dementia. Important to note, all of the cases in the meta-analytical review, as well as the primary case, had been post-mortemly studied *before* the availability of modern radiological, metabolic, neurophysiological & histiological technologies. Addressing the issue of whether LATND can be radiologically identified in a living patient, the author in reviewing recently-published brain CT, MRI, fMRI, PET and SPECT neuro-radiological studies & literature, concludes that LATND may be a valid radiological Biomarker Model in a number of progressive dementias, where deposition of neuro-toxic amyloid-beta, synuclein, tau-protein, neurofibrillary tangles, plaques and macromolecular proteinaceous prion complexes may in part reflect hippocampal injury spreading to distal locations along established limbic pathways, in association with glial scavenger and microvascular inflammatory injury and secondary loss of normal trophic metabolic processes necessary to sustain limbic connectivity and functionality. In conclusion, this combined neuropathological and neuroradiological study and review demonstrates that LATND processes can be tracked 1) neuro-radiologically, 2) through human post-mortem analysis, as well as 3) by means of the same animal models used by Papez & others in defining the Limbic Circuit.

Keywords: hippocampal limbic transneuronal degeneration, cognition, dementia

A5-07

HELMETS MAY PROVIDE PARTIAL PROTECTION AGAINST CONCUSSION: A PROSPECTIVE STUDY WITH SCAT3 AND EYE TRACKING

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Objective: Helmet use has been shown to reduce death and neurosurgical intervention, but efficacy in concussion prevention remains unknown. We hypothesized that helmet use reduces concussion effects as measured with Sport Concussion Assessment Tool 3 (SCAT3) and an eye tracking measure. Outcome measures also included hemorrhage on head CT, admission, and length of stay (LOS).

Methods: Patients involved in activity traditionally supporting helmet use were prospectively recruited and administered SCAT3 and eye tracking for 220 seconds while watching a music video. Uninjured healthy controls were recruited for comparison. Two-tailed Mann-Whitney test compared helmeted versus unhelmeted groups. Kruskal-Wallis compared distributions among helmeted, unhelmeted and control groups.

Results: 55 head trauma patients were recruited, 18 helmeted and 37 unhelmeted. There were 31 cyclists / athletes and 24 construction workers. There was no difference in hemorrhage on CT scan, admission, LOS and SCAT3 subset scores between helmeted and unhelmeted patients. SCAT3 subsets were significantly different in all trauma patients versus all controls. 42 of 89 eye tracking metrics significantly differed between helmeted and unhelmeted trauma patients versus controls. 7 of 89 eye tracking metrics were significantly worse (trending away from controls) in unhelmeted versus helmeted patients, while only 1 of 89 metrics was worse in helmeted versus unhelmeted patients.

Discussion: Helmet use was associated with less severe injury in 7 of 89 eye tracking metrics compared to unhelmeted patients, however SCAT3 subsets were not different between these groups. Limitations

include sample size and selection bias in helmet efficacy, injury severity, and pre-morbidity.

Keywords: biomarker, concussion, eye tracking, helmet

A5-08

PERIPHERAL CONCENTRATIONS OF TOTAL TAU ARE INCREASED IN MILITARY PERSONNEL WHO SUSTAIN TRAUMATIC BRAIN INJURIES DURING DEPLOYMENT

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Background: Military personnel are commonly exposed to multiple traumatic brain injuries (TBIs) during deployment, placing them at high risk for chronic symptoms. Elevated concentrations of tau are observed in blood acutely following a TBI, and accumulations within neurons and glial cells are one of the pathologic hallmarks of chronic traumatic encephalopathy. The role of tau elevations in blood in the onset and maintenance of long-term symptoms after TBI has not been investigated.

Design: Plasma total tau concentrations were measured using a novel ultra-sensitive single-molecule enzyme-linked immunosorbent assay. Classification of self-reported TBI+ subjects (n=70) versus TBI- subjects (n=28) was made using the Warrior Administered Retrospective Casualty Assessment Tool, which compiles data on war-related injury types, mechanisms, and post-injury symptoms. Group differences in tau concentrations were determined through ANOVA models, and area-under the curve determined the sensitivity and specificity of tau concentrations in predicting TBI and chronic symptoms.

Results: Concentrations of plasma tau were significantly elevated in subjects with TBI+ compared to TBI- ($F_{1,97}=4.97$, $p=0.03$). Within the TBI+ cases, plasma total tau concentrations were significantly associated with having a medical record of TBI ($F_{1,69}=6.15$, $p=0.016$), as well as reporting the occurrence of three of more TBIs during deployment ($F_{1,69}=8.57$, $p<0.01$).

Conclusion: Total tau concentrations are elevated in military personnel who report multiple TBIs, and relate to symptoms of PCD, independent of PTSD and depression. These findings suggest plasma tau shows promise as a biomarker for chronic TBI-related symptoms.

Keywords: highly sensitive immunoassays, total tau, prognostic biomarkers, chronic symptoms

A5-09

EXPLORING THE MOLECULAR OVERLAP IN THE BRAIN AND PLASMA OF TBI AND AD MOUSE MODELS USING PROTEOMIC AND LIPIDOMIC TECHNOLOGY

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Traumatic brain injury (TBI) is a major cause of disability in the military and civilian population, and for many years has been known to be a major risk factor for Alzheimer's disease (AD). Although the existence of this relationship is well recognized, and the overlap and distinction between pathological features of AD and TBI, have long been the subject of reporting and discussion, the precise nature of how TBI leads to or precipitates AD pathogenesis is currently not understood. To address this problem we are generating time-dependent molecular profiles of response to TBI and AD pathogenesis in mouse models, using proteomic and lipidomic analyses. We are using the well-validated hTau mouse models that develops age-related tau pathological features, and our well-established model of mTBI in C57BL/6 mice. Brain and plasma from these animals have been collected at different ages (for hTau mice), or at different timepoints after repetitive mTBI (C57BL/6). Liquid chromatography/mass spectrometry (LC-MS) and in source collision induced dissociation (SCID) approaches are being applied to develop molecular profiles of proteins and lipid species that are significantly differentially expressed as a consequence of AD or mTBI. We show an age-related upregulation in phosphotidylcholine (PC/ePC) and lysophosphotidylcholine (LPC) species in the plasma of both TBI and hTau mouse models. We anticipate that the exploration of molecular profiles from these animal models will enable us to identify cellular pathways that have pathogenic significance in human conditions. Moreover, we further aim to explore these identified pathways as potential targets for therapeutic intervention. Generation of Omic analyses are ongoing for comparisons of TBI profiles at 24 hrs, 3, 6, 9 and 12 months post-injury with profiles at 3, 9 and 15 months of age in the hTau models.

Keywords: concussion, Alzheimer's Disease, animal models, Omic analyses

A5-10

GFAP AND UCH-L1 DURING THE FIRST WEEK AFTER A TBI - CORRELATIONS WITH CLINICAL AND IMAGING FINDINGS AND OUTCOME

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Introduction: Protein biomarkers glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1) may help to detect traumatic brain injury (TBI), assess its severity and improve outcome prediction. We investigated the relation of the GFAP and UCH-L1 levels to the severity of TBI and to outcome during the first week after the injury.

Methods: Serum UCH-L1 and GFAP were measured from 389 patients with acute TBI and 81 controls enrolled in a multicentre prospective study. The measures included initial Glasgow Coma Scale (GCS), head CT scan and blood samples (admission and on days 1, 2, 3 and 7). The outcome was assessed using Glasgow Outcome Scale (GOS) or its extended version (GOSe).

Results: GFAP and UCH-L1 levels on admission and during the first two days after the injury correlated with the initial GCS. On admission, AUC (receiver operating characteristics) for distinguishing any pathological finding in CT was 0.739 and 0.621, for GFAP and UCH-L1, respectively. There was a negative correlation with the outcome and UCH-L1 and GFAP levels on the first three and two days, respectively. For UCH-L1 to predict unfavorable outcome ($GOS \leq 3$), incomplete recovery ($GOSe \leq 8$) or death the AUC was 0.727, 0.538 and 0.655, respectively. For GFAP the corresponding AUCs were 0.723, 0.628 and 0.716.

Conclusions: These results support the prior findings of potential role of GFAP and UCH-L1 in acute phase and prognostic diagnostics of TBI. The novel finding is that GFAP and UCH-L1 levels correlated both with the initial severity and outcome of TBI during the first two days after the injury, thus providing potentially useful information also after the day of admission.

Keywords: severity, outcome, traumatic brain injury, GFAP, UCH-L1

A5-11

A NEW PANEL OF HUMAN ASTROGLIAL NEUROTRAUMA BIOMARKERS AND TRAUMA RELEASE MECHANISMS

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Despite increasing interest in diagnostic use of traumatic brain injury (TBI) biomarkers, a clinically applicable high fidelity neurotrauma biomarker has been elusive. Large disparities in severity, progression and outcome among TBI patients demand unambiguous post-injury diagnostic monitoring to improve patient care and classification. We previously identified a panel of astroglial-enriched markers that are acutely released after mechanical trauma (Levine et al., in press). Abrupt pressure-pulse stretching of *in vitro* matured fetal human astrocytes caused severity and time-dependent marker release. A preclinical study validated the elevation of six, highly correlated astroglial markers in biofluid samples of 25 TBI patients compared with 11 healthy subjects. Sensitive immunoblotting with scaled densitometry and pure protein quantification measured markers in raw cerebrospinal fluid (CSF) as well as serum and plasma depleted of abundant proteins. While CSF levels of known astroglial markers GFAP and S100b significantly decreased during the first week post-injury, four additional astroglial proteins remained comparatively stable during the same time-period after TBI. Astroglial-release markers correlated with the presence of a serum-specific protein in CSF, suggesting post-injury brain bleeding associated with astroglial injury. A CSF marker was dramatically decreased after TBI and levels recovered over subsequent post-injury days. Importantly, four astroglial-released markers were consistently elevated in blood samples of TBI patients versus Controls. In conclusion, this new panel of human astroglial TBI biomarkers shows *in vitro* defined release mechanisms, is acutely elevated in TBI patients and is detectable in blood. Combined, this work identifies a brain-specific panel of neurotrauma biofluid markers with diagnostic potential.

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Keywords: cerebrospinal fluid, in vitro trauma model, human glia, serum, plasma

A5-12

EVALUATION OF THE EXTRACELLULAR MATRIX AS A SOURCE OF BIOMARKERS FOR INJURY SEVERITY WITHIN 24 HOURS OF DIFFUSE BRAIN INJURY

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The extracellular matrix (ECM) provides structural support for neuronal, glial and vascular components of the brain, and regulates intercellular signaling required for cellular morphogenesis, differentiation and homeostasis through constant remodeling. We hypothesize that the ECM is susceptible to degradation and accumulation of glycoproteins, which serve as biomarkers specific to diffuse brain injury severity and region. Experimental TBI was induced in male Sprague Dawley rats (325–375 g) by midline fluid percussion injury (FPI) at sham (n = 6), mild (1.4 atm, n = 16) and moderate (2.0 atm, n = 16) severity. Tissue from the cortex, hippocampus and thalamus was collected at 1, 3, 7 and 14 days post-injury. All samples were quantified by western blot for glycoproteins: reelin, fibronectin, laminin, and tenascin-c. Band intensities were normalized to sham and relative to β-actin. In the hippocampus, fibronectin increased over 1 and 3 days post-injury at mild and moderate severity, returning to sham levels by 7 days post-injury. Tenascin-c increased at 7 and 14 days post-injury. Based on the observed changes, we investigated the onset time course of ECM glycoprotein expression at 15 minutes, 1 and 2 hours post-injury in mild and moderate diffuse TBI. Results show significant decreases in fibronectin for mild injury at 15 minutes in the thalamus, and at 15 minutes and 2 hours in the cortex. Reelin was decreased in the hippocampus at all three time points. Changes in levels of these glycoproteins at acute time points suggest that they may be useful diagnostic biomarkers in an emergency room setting. The specificity and sensitivity of these biomarkers remain to be validated as clinically useful tools.

Funding: Translational Collaboration Grant PCH-ASU; PCH Mission Support Funds

Keywords: Biomarker, Extracellular Matrix, Emergency Medicine

A5-13

OPERATION BRAIN TRAUMA THERAPY (OBTT): SERUM-BASED BIOMARKER INVESTIGATION IN A MICROPIG FLUID PERCUSSION INJURY MODEL

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As part of the consortium-based OBTT study, 16 micropigs were subjected to mild TBI involving sham or central fluid percussion injury (cFPI). Serial blood samples were obtained pre-craniotomy and post-craniotomy, as well as at 1 min, 30 min, 1h, 3h, and 6h post-injury. All blood samples were processed to obtain serum following OBTT standard operations for detailed biomarker analysis.

Four biomarker assays were run, including neuronal biomarker UCH-L1, astroglia biomarker GFAP, microglial biomarker Iba-1 and neuroinflammatory biomarker interleukin-6 (IL-6). Serum

GFAP levels were elevated in post-injury samples from all 13 injured micropigs. GFAP levels appear to be elevated as early as 1–30 min after injury, but 1–6 hr post-injury samples have the highest GFAP elevations overall. GFAP levels were elevated to a much lesser extent in the sham-operated micropigs. Serum UCH-L1 profiles in micropigs appears more complex. Four of 16 micropigs have high baseline pre-surgery serum UCH-L1 levels (>200 pg/mL) and 5 micropigs have no detectable UCH-L1 signal either pre-surgery or after injury. Serum Iba-1 levels are modestly elevated post-injury in only 4 of 12 animals at one or more time points and elevated post-sham operation in one of 3 animals. Lastly, IL-6 levels were significantly elevated in 9 of 11 animals with cFPI at one or more post-injury time points.

Group analysis showed post-injury GFAP levels significantly elevated at 1, 3 and 6h post–injury when compared to pre-injury controls. There is also a trend of IL-6 increase following FPI. Taken together, we have identified and characterized several biomarkers with potential use for future screening of therapeutic agents in this micropig model.

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Keywords: fluid percussion injury

A5-14

A SYSTEMATIC RAT SPINAL CORD INJURY BIOMARKER STUDY AND TEMPORAL BIOMARKER PROFILING IN TWO BIOFLUID TYPES

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In the United States, there are approximately 12,000 new cases of spinal cord injury (SCI) each year and some 1.2 million people living with paralysis due to SCI. However no effective therapy to treat acute SCI is available. Here we report a systematic rat SCI biomarker study examining the effects of injury severity and temporal profiling of eleven SCI candidate biomarkers in two biofluid types (cerebrospinal fluid (CSF) and serum). We utilized an established rat thoracic contusive spinal cord injury model with either moderate or severe injury. CSF and serum samples were obtained at 4, 24 hr, and 7 day post-injury. Candidate biomarkers we focused on included axonal injury markers αII-spectrin breakdown products (SBDPs), neuronal cell body injury marker UCH-L1, gliosis/glial injury markers S100β & GFAP and GFAP-BDPs, demyelination marker MBP, neuroinflammation marker IL-6 and autoantibodies to GFAP and spinal cord protein. Our results shows three biomarker pattern types: (i) biomarkers that are severity-dependently elevated in both CSF and serum at acute time points (4 – 24 h) – SBDPs, GFAP, G-BDPs, S100b and UCH-L1; (ii) biomarker that is only elevated in serum (4–24 h) but not CSF - IL-6, suggesting a systemic response to SCI; (iii) biomarkers that appear not elevated in either biofluid after SCI - MBP and autoantibodies. These results not only allow us to gain important insight into the pathomechanisms of SCI, but our learning from them will directly translate into human SCI studies.

Keywords: SCI, biomarkers, spectrin, GFAP, S100b, UCH-L1

A5-15

HUMAN SPINAL CORD INJURY CSF AND SERUM BIOMARKER STUDY

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Spinal cord injury (SCI) is a devastating insult and frequently occurs in young men and women as a result of accidents during sports and other activities. It also has high frequency in the military among servicemen. In these cases, SCI can result from blast injuries or high velocity metal fragments. There are of an estimated 12,000 new cases of SCI in the United States annually and approximately 1.2 million people living with paralysis due to SCI. Although much information has been gained from experimental and clinical studies elucidating injury mechanisms and the testing of new treatments to target spinal cord injury, no clinically effective treatments are currently available to treat SCI. The heterogeneous nature of spinal cord injury may require customized therapies specific for selective injuries and subjects. We hypothesize that it will be extremely advantageous if biomarkers sensitive to injury severity and treatment responses can be identified.

Here we report a systematic human SCI biomarker study examining the effects of injury severity and temporal profiling of eleven (11) SCI candidate biomarkers in both cerebrospinal fluid (CSF) and serum. Serial CSF and serum samples were obtained from 14 SCI patients with initial ASIA score (AIS) of A-B at every 6 hours for up to 6 days. SCI biofluid and control CSF (n = 20) and serum (n = 20) samples were subjected to immunoblotting and/or immunoassays for protein biomarker levels. Candidate biomarkers included axonal injury markers αII-spectrin breakdown products (SBDP150, SBDP145 & SBDP120), neuronal cell body injury marker UCH-L1, gliosis/glial injury markers S100β, GFAP and GFAP-BDPs, demyelination marker MBP, neuroinflammation marker IL-6 and autoantibodies to GFAP and spinal cord proteins. Our key findings are as follows. (i) All brain-derived protein biomarkers are elevated in the acute phase CSF and serum samples from SCI patients when compared to corresponding normal controls. (ii) CSF GFAP-and GFAP-BDP levels (and to a lesser extent S100b) shows a strong SCI severity correlation. (iii) Elevation of both CSF UCH-L1 and SBDPs are detected in almost all SCI subjects. Notably, CSF UCH-L1 shows some unique and late rises (day 4–5) in a subset of patients. (iv) Of all the serum markers, GFAP levels has the best correlation with SCI severity (AIS), followed by S100b and SBDP150. (v) Serum UCH-L1 tends to peak early post-injury but also shows sustained levels in some patients on day 4–6. IL-6 rises acutely in most SCI patients, but its levels appear independent of SCI severity. Lastly, Anti-GFAP and anti-spinal cord proteins (IgM, IgG) shows a time-dependent elevation (from day 0 to 6) in serum and to a lesser extent in CSF in subset of SCI patients, regardless of their injury severity. These human SCI biomarker results allow us to gain important insight into the pathomechanisms of SCI. Our results will expand into further human SCI studies by not only confirming the utilities of biomarkers in monitoring human SCI progression or recovery but also guiding personalized therapeutic and rehabilitation strategies.

Supported by grant W81XWH-12-1-0277 from the United States Army

Keywords: theranostic, GFAP, IL-6, UCH-L1, spinal cord injury

A5-16

PROTON MAGNETIC RESONANCE SPECTROSCOPY PREDICTORS OF TISSUE LOSS AFTER TRAUMATIC BRAIN INJURY

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Similar injuries among patients with traumatic brain injury (TBI) can lead to a wide variety of pathological and clinical outcomes. Biomarkers that predict injury progression could help elucidate mechanisms of secondary injury and lead to strategies that mitigate their effects. Experimental models of TBI have shown heterogeneity with regards to tissue loss measured using T2-weighted MRI and histopathology, despite the same initial parameters. An early neurochemical profile of metabolic injury can be measured *in vivo* using proton magnetic resonance spectroscopy (^{1}H -MRS). Our goal was to determine whether the spectroscopic profile of early TBI could predict subsequent tissue loss.

We used a controlled cortical impact over the sensorimotor cortex in adult male rats. High field ^{1}H-MRS was obtained from 1) a cortical voxel proximal to the site of impact and 2) an underlying hippocampal voxel at one hour (D0), one day (D1) and three days (D3) post injury. We then obtained T2-weighted MRI at 14 days and measured the amount of tissue loss by comparing the volume of preserved tissue in the ipsilateral hemisphere versus the contralateral side. Statistical significance was determined using correlation analysis.

We found significant correlations between several cortical and hippocampal ^{1}H-MRS biomarkers and tissue loss at 14 days, however, the predictive metabolic profiles varied between the two regions. The strongest predictors in hippocampus were lactate on D0, aspartate on D1 and n-acetyl aspartate on D3. The strongest predictors in cortex were phosphocreatine on D1 and glucose on D3.

These results show that ^{1}H-MRS can predict injury progression, not only when measured in visibly injured tissue but also in radiographically normal tissue adjacent to the injury site. If translated to human use, these biomarkers could provide clinicians with predictors of injury severity and targets for early intervention.

Keywords: Spectroscopy, TBI, CCI

A5-17

COMPARISON OF SYSTEMIC INFLAMMATORY PROFILES IN HEALTHY ATHLETES WITH AND WITHOUT A HISTORY OF CONCUSSION

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Background: Chronic effects of concussion, a form of mild traumatic brain injury (mTBI), are not well understood. The injury triggers activation of central and peripheral immune cells with the infiltration of neurological tissue and release of multiple inflammatory mediators. It has also been hypothesized that a dysregulated immune response may underlie the etiology of chronic health conditions. Therefore, evaluating immune markers in the peripheral blood may provide useful information reflecting brain immunopathology.

Objective: To compare circulating profiles of inflammatory markers in uninjured athletes with and without a history of concussion.

Methods: Peripheral blood was sampled from 50 uninjured athletes ($n=35$ male; $n=15$ female), stratified into two groups based on previous concussion history ($n=23$ yes; $n=27$ no). Relevant medical history was obtained during pre-season by Sport Concussion Assessment Tool 3. An ultra-sensitive MULTI-ARRAY® immunoassay platform was used to assess plasma concentrations (pg/ml) of 19 cytokines (e.g., including: interleukin (IL) – 6, tumor necrosis factor (TNF) –α, –β); and 10 chemokines (e.g., macrophage inflammatory protein (MIP) –1α, –1β, monocyte chemoattractant protein (MCP) –1, –4, macrophage derived chemokine (MDC), thymocyte- and activation-regulated chemokine (TARC), and interferon gamma-induced protein (IP) –10).

Results: Significant elevations of the cytokine IL-6 ($p=0.003$), and the chemokines IP-10 ($p=0.002$) and MCP-4 ($p=0.02$), were observed in healthy uninjured athletes with a history concussion compared with those who had no previous concussions.

Conclusion: Athletes with a history of concussion display an altered systemic inflammatory profile compared to athletes with no previous concussions. While chronic low-grade inflammation is generally considered a health detriment, the role of the inflammatory response following concussive injury, with respect to long-term neuroprotective or neurodegenerative effects remains unclear.

Keywords: Mild Traumatic Brain Injury, Concussion, Sport

A5-18

MULTIVARIATE BIOMARKER PROFILING, SENSORY MOTOR DEFICITS, CONSCIOUSNESS AFTER SINGLE AND REPEAT PROJECTILE CONCUSSIVE INJURY

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Developing diagnostic and prognostic biomarkers for mild traumatic brain injury (mTBI) has become an urgent medical need. The purpose of this study was to evaluate and correlate the effects of single and repeated mTBI on consciousness, sensory-motor deficits, and CSF biomarker abundance. The projectile concussive impact (PCI) model was used to induce mTBI. Anesthetized rats received single (1XPCI) or repeated (2-4XPCI) impacts with 1h intervals. Matched controls (sham) received anesthesia alone. Righting reflex (RR) was determined immediately; sensory-motor deficits (revised neurobehavioral severity scale, NSS-R) were recorded after 45 min. CSF was collected 1h after the last impact and GFAP, UCH-L1, and Tau were analyzed by ELISA. Key findings of average biomarker levels, behavioral scores ($p \leq 0.05$, vs. Sham) or correlations ($p \leq 0.05$, Spearman r) are reported. Results confirmed significant PCI-induced increases in RR and composite NSS-R scores. Among individual NSS-R components, 1XPCI significantly increased drop and righting scores; only 4XPCI increased the hind-paw sensory deficit. Levels of GFAP in CSF rose to 5.47 ng/mL (1XPCI), 8.22 ng/mL (2xPCI), 2.97 ng/mL (3XPCI), and 5.24 ng/mL (4XPCI). Tau was increased to 7.59 ng/mL (2XPCI)

or 11.07 ng/mL (4XPCI). UCH-L1 peaked at 615.49 ng/mL (2XPCI). Interestingly, there was strong correlation between GFAP and Tau ($r=0.89$) in 4XPCI cohorts. UCH-L1 correlated to Tau after 1XPCI ($r=0.72$) and 3XPCI ($r=0.98$). Among all PCI cohorts, Tau and UCH-L1, but not GFAP, correlated to RR ($r=0.41$ and 0.30, respectfully) as well as to composite NSS-R ($r=0.30$ and 0.39, respectfully). Both Tau and UCH-L1 aligned with tail reflex deficits ($r=0.36$–0.40), whereas Tau specifically correlated to ear-pinch response deficits ($r=0.43$) and increased UCH-L1 was in concert with sound response deficits ($r=0.36$). These results suggest that single and repeated PCI are associated with specific CSF derived biomarkers and neurological deficits, which may lead to critical understanding the differential effects between single or repeated concussions.

Keywords: Mild TBI, Concussion, CSF, GFAP, Tau, UCH-L1

A5-19

INVESTIGATION OF PUTATIVE ACUTE SERUM DIAGNOSTIC BIOMARKERS IN A PROJECTILE CONCUSSIVE IMPACT INJURY

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Investigation of microRNAs (miRNAs) as putative biological indicators of injury has been examined in many disease states. MiRNAs regulate many cellular processes through translational repression or degradation. In this study we used the projectile concussive impact (PCI) model and microarray platform to examine whether miRNAs may serve as indicators of mild traumatic brain injury (mTBI). This injury model represents a mild clinically relevant injury. Briefly, PCI injury induction is a non-invasive, closed-head blunt impact to the right temporoparietal region. Sham animals received equivalent anesthesia without impact. Serum was collected from rodents at 4h and 1d following injury and miRNA dysregulation was measured in rodents. MicroRNA arrays were performed using Taqman megaplex reverse transcription and pre-amplification kits. Each animal was run as a single independent array ($n=10$/group). We limited our reporting to miRNAs with p value <0.05 and a two-fold or greater change. Given these criteria, we found one miRNA (miR-350) was significantly decreased by 2.5 fold 4h post PCI. At 1d post PCI, four miRs were upregulated including miR-Let 7f (2.1 fold), miR 190 (2.7 fold) and miR 199a (7.4 fold). Interestingly, miR 350, which was initially suppressed, was significantly increased nearly 3 fold at 1d post PCI. These serum miRNA changes will be further studied to determine their usefulness as both diagnostic and prognostic indicators of mTBI. Additional studies will determine the temporal profile of miRNA changes up to 7d post injury and whether specific miRNAs may serve prognostic and/or theragnostics markers of mTBI at later time points post-injury.

Keywords: microRNA, mild TBI, array

A5-20

DISCOVERING PROGNOSTICATORS FOR REPEATED CONCUSSIONS: A GLOBAL METABOLOMIC STUDY

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Mild concussive injury can lead to a series of biochemical sequelae that renders the brain vulnerable to a second concussion. Critically, the time interval between the initial and the second concussion determines the risk of exacerbated outcome. To test this hypothesis, this study evaluated the effects of repeated concussions occurring at variable intervals on biochemical alterations using global metabolomics. Rats received two consecutive projectile concussive impacts ($2\times$PCI) at 6h, 24h, or 7d intervals; each paired with a procedure-matched sham controls (anesthesia only). Cerebral cortices and cerebrospinal fluid (CSF) were collected at 2h following the second PCI ($n=7$/group). Metabolic profiling detected a total of 447 and 404 biochemicals in brain tissue and CSF respectively. The percentage of biochemicals that were significantly altered following $2\times PCI_{6}$h, $2\times PCI_{24h}$, and $2\times PCI_{7d}$ were 20.4%, 21.3%, 15.0% in the brain ($p<.05$ vs. sham), and 23.3%, 7.4%, 5.0% in the CSF ($p<.05$ vs. sham). These results suggest a differential threshold of the brain vs. the CSF in response to concussion intervals with regards to the number of biochemical alterations. Most notably, putrescine, a polyamine involved in endogenous tissue repair, showed the best prognostic potential among all metabolites due to its high specificity to the incidence interval of concussion. Cerebral putrescine levels, possibly triggered by the injury for cellular regeneration, were significantly increased ($p<0.05$) and negatively correlated with the concussion intervals (i.e. shorter interval resulted in higher putrescine level; $R^2=0.6$). As intracellular putrescine accumulated to potentially toxic levels in brain tissue, its extracellular form, acetylputrescine, was released into the CSF, leading to its elevation in both the brain and the CSF and echoing the observed alterations of intracellular putrescine in the same animals. Further, linear regression indicates that cerebral acetylputrescine increased as the interval between concussions shortened ($R^2=0.6$). Overall, these findings warrant further investigation on the abundancy of putrescine associated metabolites in the periphery circulation, hence the feasibility of developing a reliable prognosticator(s) for concussion.

Keywords: Metabolomics, Concussion

A6 Poster Session II - Group A: Edema

A6-01

ACUTE HYDROCEPHALUS IN CERVICAL SPINAL CORD INJURY: TWO DISTINCT PATHOPHYSIOLOGIC CAUSES AND LITERATURE REVIEW

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Cervical spinal cord injury (SCI) has well-known risks of clinical decline from medical complications or less frequently, ascending spinal deficits. Intracranial pathology, i.e., hydrocephalus, secondary to cervical SCI however is extremely rare. We discuss two patients who developed acute altered mental status and hydrocephalus following cervical spine fracture with SCI. A literature review was performed using PubMed: Medline to search for similar cases. Patient A, a 40 year-old male, presented with Glasgow Coma Scale of 11T and C4 complete SCI following a C4-5 fracture-dislocation. Twelve hours after urgent posterior decompression and fusion, the patient became acutely comatose. Head CT revealed moderate hydrocephalus and posterior fossa edema. Ventriculostomy did not provide neurologic improvement. MRI revealed acute ischemic stroke of the brainstem and cerebellum with tonsillar herniation. Review of pre-operative MRI of the c-spine is highly suggestive of bilateral vertebral artery occlusion due to absent flow voids. Patient B, a 53 year old male, presented with an incomplete

C7 SCI from a type II odontoid fracture with extensive C1-2 ligamentous injury as well as very minimal frontal lobe contusions. On post injury day 3, the patient became nonresponsive with a head CT demonstrating new moderate hydrocephalus despite a negative CTA head/neck. Emergent ventriculostomy revealed high pressure, but did not produce neurologic improvement. Of note, c-spine MRI performed approximately 12 hours prior to clinical decline demonstrated severe edema of the spinal cord ascending from a focus at C5-6 to the cervicomedullary junction. Literature search revealed 4 case reports of hydrocephalus following SCI. Two mechanisms have been proposed including a communicating hydrocephalus from traumatic blood ascending in the subarachnoid space and non-communicating hydrocephalus from ascending edema causing a 4th ventricular outlet obstruction at the foramina of Lushcka and Magendie. The two suspected mechanisms in the present cases: vertebral artery obstruction resulting in cerebellar infarction, edema and herniation with 4th ventricular obliteration; and ascending cord and brainstem edema resulting in 4th ventricular outlet obstruction.

Keywords: Acute hydrocephalus, Spinal cord injury, Vertebral artery injury, Spinal cord edema

A6-02

CILOSTAZOL ATTENUATES BLOOD-BRAIN BARRIER DISRUPTION AND SUBSEQUENT SECONDARY CELLULAR DAMAGE FOLLOWING CORTICAL CONTUSION IN RATS

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Objective: Cerebral contusion results in tissue damage from primary (mechanical) and subsequent secondary (neurochemical) processes. Our previous studies have demonstrated that regional cerebral blood flow (rCBF) markedly decrease by microthrombosis formation that underlie these secondary processes and represent potential targets for therapeutic intervention. Meanwhile, the hemorrhagic lesion results in cortical contusion often progresses during the several hours following injury. Cilostazol has anti-plated aggregation effect, anti-thrombosis effect, and vasoconstriction effect. The aim of the present study were to examine whether cilostazol can attenuate secondary brain injury, and whether cilostazol prevent hemorrhagic progression following cortical contusion. The effect of cilostazol on the volume of the cavity formation, and the influence of cilostazol on hemorrhagic progression were tested employing a cortical contusion model in rats.

Methods: Contusion injury was induced with a controlled cortical impact (CCI) device in the parietal cortex of 30 male Wistar rats under anesthesia. The animals were randomly divided into 3 group and orally given cilostazol (30 mg/kg), aspirin (20 mg/kg) and vehicle (control) 1 hour before CCI, and were sacrificed for making evaluations of microthrombosis formation and extravasation of Evans Blue dye (EBD) at 48 hours post injury and for the measurements cavity formation at 14 days.

Results: The cavity formation decreased in cilostazol ($5.918 \pm 1.269\ mm^3$) (mean ± SD) relative to controls ($7.083 \pm 2.052\ mm^3$), whereas aspirin markedly increased (11.093 ± 2.585 mm3, $P < 0.05$). Hemorrhagic progression and the measurement of EBD extravasation reduced in cilostazol (1.460 ± 0.401 mm3) relative to aspirin (7.189 ± 0.747 mm3, $P < 0.05$). The microthrombosis formation in the peripheral areas of the contusion was significantly attenuated by cilostazol (control: 757.2 ± 46.0 pics/$0.25\ mm^2$ vs. cilostazol: 80.1 ± 4.8 pics/$0.25\ mm^2$, $P < 0.05$).

Conclusions: Cilostazol may have a therapeutic potential to prevent microthrombosis formation without hemorrhagic complication and for attenuating changes vascular permeability within areas the surrounding contusion.

Keywords: cerebral contusion, secondary cellular damage, microthrombosis formation, cilostazol

A6-03

APOE GENOTYPE AND ACUTE EDEMA FORMATION FOLLOWING EXPERIMENTAL TRAUMATIC BRAIN INJURY

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APOE4 genotype has been associated with prolonged coma, increased mortality and worsened outcome following traumatic brain injury (TBI). Injury-induced edema and resulting increased intracranial pressure (ICP) is one of the most serious complications of TBI and is associated with adverse outcome. To determine whether Apolipoprotein E (ApoE) plays a role in edema formation after injury and whether this is influence by APOE genotype, we exposed ApoE wildtype (WT), ApoE knockout (KO), and human APOE3 or APOE4 overexpression (GFAP-APOE3, GFAP-APOE4) mice to the controlled cortical impact (CCI) model of TBI or sham injury and assessed water content in the ipsilateral hippocampus and cortex 24h after injury using the wet weight/dry weight method. Exposure to CCI increased water content in the ipsilateral cortex of all genotypes 24h after injury ($p < 0.05$ compared to sham, unpaired t-test, within genotype comparison). However, water content in the ipsilateral hippocampus was only increased after CCI in GFAP-APOE4 mice compared to sham ($p < 0.05$, unpaired t-test, within genotype comparison), suggesting an APOE-genotype effect on edema formation in the hippocampus after injury. Further, while hippocampal water content not differ in sham mice between genotypes, cortical water content was reduced in GFAP-APOE3 sham mice compared to WT, KO, and GFAP-APOE4 sham mice ($p < 0.01$-$p < 0.05$, one-way ANOVA w/Tukey post-hoc), suggesting that APOE genotype may have an effect on inherent brain water content levels. Our preliminary data supports previous observations that ApoE status affects edema formation after brain injury and, for the first time, shows an APOE genotype-specific effect on injury-induced edema formation in the hippocampus.

Keywords: APOE, Transgenic mice, Hippocampus, Acute injury

A7 Poster Session II - Group A: Endocrine

A7-01

EXPERIMENTAL DIFFUSE BRAIN INJURY LEADS TO CHRONIC CORTICOSTERONE DYSFUNCTION WITH EVIDENCE OF COMPROMISED NEURON MORPHOLOGY

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As many as 20–55% of patients with a history of traumatic brain injury (TBI) experience chronic endocrine dysfunction, leading to impaired quality of life, impeded rehabilitation efforts, and lowered life expectancy. Endocrine dysfunction after TBI is thought to result from acceleration-deceleration forces to the brain within the skull, creating enduring hypothalamic and pituitary neuropathology, and subsequent hypothalamic-pituitary (HP)-axis dysfunction. These experiments were designed to test the hypothesis that a single diffuse TBI results in chronic dysfunction of corticosterone (CORT), a glucocorticoid released in response to stress, with evidence of structural damage to the HP-axis. We used a rodent model (adult, male Sprague-Dawley rats) of diffuse TBI induced by midline fluid percussion (mFP). At 2 months post-injury, circulating levels of CORT were evaluated at rest, under restraint stress and in response to dexamethasone, a synthetic glucocorticoid commonly used to test HP-axis regulation. Further, we assessed changes in injury-induced neuron morphology (Golgi stain) and neuropathology (silver stain) in the paraventricular nucleus (PVN) of the hypothalamus. Resting plasma CORT levels were decreased by $\sim$60% at 2 months post-injury, concomitant with altered complexity of neuron processes in the PVN over time. Results provide evidence that a single moderate diffuse TBI leads to hormonal and structural changes, as it pertains to the HP-adrenal axis, that can contribute to the persistence of endocrine dysfunction. Future experiments aim to evaluate additional HP-related hormones and anatomical pathology that will support mFP-induced diffuse TBI as a model of TBI-induced chronic endocrine dysfunction.

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Keywords: Corticosterone, Diffuse TBI, Neuron morphology, Endocrine Dysfunction

A7-02

A PROSPECTIVE EVALUATION OF NEURO-ENDOCRINE AND NUTRITION ABNORMALITIES FOLLOWING SEVERE TRAUMATIC BRAIN INJURY IN ADULT PATIENTS

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Neuro-endocrine dysfunction after traumatic brain injury (TBI) has previously been reported to occur in 15–90% of patients in small patient series. In this study, we evaluate the prevalence of acute neuro-endocrine and nutrition dysfunction following severe TBI in a large single-center, prospective cohort. Neurological outcome was measured by the Glasgow Outcome Scale (GOS) score at 6-month and 12-month post-TBI. Over a 6 year period (2009–2014) endocrine and nutrition data was collected for 234 patients (mean age 42.9 $\pm$ 18.1 years, 77.4% male, initial Glasgow Coma Scale score $\leq$8, Injury Severity Scale 27.6 $\pm$ 11.5). T3, total protein, albumin and testosterone (male only) were predominantly low in 61.5%, 72.2%, 59.4%, and 97.1%, respectively. Random serum cortisol and prolactin were predominantly elevated in 86.9% and 56.3%, respectively. 6 month post-TBI GOS revealed that 26.6% of patients had a good outcome (GOS 4–5) and 73.4% of patients had a poor outcome (GOS 1–3). 12 month GOS resulted in 27.1% good outcome and 72.9% poor outcome. When comparing change between first and last measurement with 6 month GOS, total protein and albumin were significant (p 0.008 and 0.013, respectively). At 12 months, total protein and free T3 were significant (p 0.002 and 0.015, respectively). Spearman correlation between outcome and last measured value were significant at 6 month GOS in total protein ($p < 0.0001$), albumin ($p < 0.001$) and cortisol (p 0.075), and 12 month GOS in total protein ($p < 0.0001$) and albumin ($p < 0.001$). Our results are consistent with previous literature demonstrating that neuro-endocrine and nutrition abnormalities are frequent after severe TBI, and are associated with poor outcome. These findings further support that neuro-endocrine disturbances may be important clinical targets in the management of severe TBI.

Keywords: traumatic brain injury, pituitary function, hormone deficiency, nutrition, neuro-endocrine

A7-03

ENDOCRINE DYSFUNCTION AND PITUITARY AUTOIMMUNITY IN CRITICAL AND NEUROCRITICAL ILLNESS

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Critical illness induces an activation of neuroendocrine system possibly related to inflammatory response. Aim of this study was to investigate the occurrence of neuroendocrine dysfunction in patients admitted to ICU for sepsis, traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), and in a group of patients evolving to brain death (BD).

Methods: Post-hoc analysis of prospectively collected data. Blood samples were collected for determination of TSH, fT3, fT4, ACTH, cortisol, prolactin, GH, IGF-I, and copeptin (at day 1, 2, 3 in sepsis, TBI, SAH, and at the time of BD diagnosis). Antipituitary antibodies (APA) were evaluated by an optimized IFI method on cryostat section of monkey pituitary gland. Cytokine analysis was performed with Bioplex technology. Comparison between groups was performed with ANOVA and post hoc analysis.

Results: 113 patients (36 septic, 25 TBI, 21 SAH, 31 BD) were studied. There was an high prevalence of endocrine dysfunction with specific profiles: septic patients showed the highest level of copeptin and the lowest of cortisol, FT3 and FT4. We observed in TBI an appropriate activation of cortisol axis, high copeptin and IL6 and central hypothyroidism and in BD very low copeptin due to diabetes insipidus and severe inflammatory response. IL6 level in the four groups were, respectively: 491 $\pm$ 1434, 257 $\pm$ 263, 183 $\pm$ 315, 829 $\pm$ 1269, and APA were detected in 0, 40, 14, and 16%, respectively.

Conclusions: Pituitary gland is a target of autoimmunity only in neurocritical illnesses. The neuroendocrine dysfunction related to the inflammatory reaction exibited a specific profile in the different critical illnesses. For the first time we have shown the presence of APA within 24 hours of acute brain injury, possibly interpreted as a marker of early inflammation after TBI.

Keywords: neurocritical care, critical care, endocrine dysfunction, pituitary antibodies, sepsis, inflammation

A8 Poster Session II - Group A: Regeneration & Plasticity

A8-01

PHARMACOLOGICAL MANIPULATION OF MTOR ACTIVITY TO MODULATE MALADAPTIVE INTRASPINAL PLASTICITY AND AUTONOMIC DYSREFLEXIA

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Manipulating the activity of the mammalian target of rapamycin (mTOR) after experimental spinal cord injury (SCI) is reported to increase intraspinal sprouting and functional recovery. Our published evidence correlates post-traumatic maladaptive plasticity of both primary afferents and ascending propriospinal neurons with the development of autonomic dysreflexia (AD) after complete high thoracic (T4) SCI. Therefore, we are now testing the hypothesis that pharmacologically targeting mTOR can modulate maladaptive neuronal plasticity underlying AD. We are testing specifically whether prolonged post-injury treatment with the antibiotic, rapamycin (RAP), impedes intraspinal neuronal plasticity by inhibiting mTOR and, consequently, mitigates the development of AD. Alternatively, prolonged post-injury treatment with bisperoxovanadium (bpV(pic) should disinhibit mTOR activities to promote maladaptive plasticity and exacerbate AD. We are employing pharmacological and cardiophysiological methodologies we've used to document the palliative effects of gabapentin treatment on the incidence and severity of AD. Based on FDA approval of RAP, if therapeutic efficacy is shown in our SCI model then clinical translation is tenable as a potential prophylactic treatment to abrogate AD. Initial data on the time course of phosphorylated mTOR (p-mTOR) expression in critical spinal cord segments from naive tissues or at 3, 10 and 21 days post SCI (n = 2–3/group) showed that there is an approximate two-fold increased expression after 10 days that trends back to naïve levels by 21 days. In contrast, compared to 10 days, p-mTOR expression levels were elevated after 21 days in rats that received colorectal distension (CRD) to induce AD before euthanasia. Alternatively, following prolonged RAP or bpV(pic) treatment (n = 2–3/group), both mTOR and p-mTOR expression profiles in spinal cord segments are being assessed comparatively. Moreover, proteins related to sprouting/synaptogenesis/inflammation/injury will be evaluated by measuring Akt/PKB, p70 S6, synaptophysin, PSD-95, VGlut2, c-Fos, p-NR1, IL-1b, ATF3, TSP4 and a2d1 receptor levels to establish correlations between such expression profiles and the incidence and severity of spontaneous and/or experimentally induced AD.

Keywords: Autonomic Dysfunction, Spinal cord transection, Rapamycin, Bisperoxivanadium, Sprouting

A8-02

IN VIVO REPROGRAMMING REACTIVE GLIA INTO IPSCS TO PRODUCE NEW NEURONS IN THE CORTEX FOLLOWING TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) results in a significant amount of cell death in the brain. Unfortunately, the adult mammalian brain possesses little regenerative potential following injury and little can be done to reverse the initial brain damage caused by trauma. There is a large number of reactive glia surrounding the injury area following TBI. Reprogramming adult cells to generate induced pluripotent stem cell (iPSCs) has opened new therapeutic opportunities to reprogram these reactive glia to neural fate for possible cell-replacement therapy in vivo. In this study we show that four retroviral mediated transcription factors, Oct4, Sox2, Klf4 and c-Myc, expressed in the reactive glial cells and cooperatively reprogrammed infected glia into iPSCs in the adult neocortex following TBI. These iPSCs further differentiated into a large number of neural stem cells, which further differentiated into neurons and glia in situ, and filled up the tissue cavity induced by TBI. The induced neurons showed a typical neuronal morphology with axon and dendrites, and exhibited action potential. The glia were preferentially astrocytes and oligodendrocytes, but not microglia. Our results report a strategy to convert a non-neurogenic cortex into a neurogenic region, one that can be potentially developed for brain repair through reprogramming reactive glia resident in the injury area following brain injury.

Keywords: Reprogramming in vivo,, iPSC, reactive glial, neuron, Traumatic brain Injury,

A8-03

TRAUMATIC BRAIN INJURY SEVERITY AFFECTS NEUROGENESIS IN ADULT MOUSE HIPPOCAMPUS

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Traumatic brain injury (TBI) has been proven to enhance neural stem cell (NSC) proliferation in the hippocampal dentate gyrus (HDG), which provides a potential approach to repairing the damaged brain by increasing neurogenesis. However, various groups reported contradictory results on whether TBI increases neurogenesis, partially due to a wide range in the severity of injury seen with different TBI models. To address whether the severity of TBI affects neurogenesis in the injured brain, we assessed neurogenesis in mouse brains receiving different severities of cortical impact with the same injury device. The mice were subjected to mild, moderate, or severe TBI by a controlled cortical impact (CCI) device. The effects of TBI severity on neurogenesis were evaluated at three stages: NSC proliferation, immature neurons, and newly generated mature neurons. The results showed that mild TBI did not affect NSC proliferation or neurogenesis. Moderate TBI promoted NSC proliferation without increasing neurogenesis. Severe TBI increased both NSC proliferation and neurogenesis. Our data suggest that the severity of injury affects adult neurogenesis in the hippocampus, which may partially explain the inconsistent results of different groups regarding neurogenesis following TBI. Further understanding the mechanism of TBI-enhanced neurogenesis may provide a potential approach for using endogenous NSCs to protect against neuronal loss after trauma.

Keywords: Neurogenesis, Neural stem cell proliferation, Traumatic brain injury, Injury severity

A8-04

FIX THE LESION OR KEEP BRAIN DEVELOPMENT GOING? NEUROBLAST PATTERNS AFTER TBI IN THE IMMATURE GYRENCEPHALIC BRAIN

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In rodents, neuroblasts generated in the subventicular zone have been shown to migrate through gray matter to cortical lesions where they aid in neural repair; however, it is not yet known if neuroblasts target traumatic lesions in the immature gyrencephalic brain. Here we quantify neuroblasts at the injury site (rostral gyrus) where both gray matter and white matter are damaged, and at a distant, non-injured site undergoing active population by neuroblasts (insular cortex). Piglets (postnatal day 7; N = 23) received a cortical impact to the rostral gyrus or sham surgery and bromodeoxyuridine (BrdU) before or after injury.

Brains were collected 7 days post-injury. In this interim analysis, neuroblast density was greater in the rostral gyrus gray matter in injured piglets with no effect on $BrdU^+$ or $BrdU^+$/doublecortin$^+$ (DCX) cells. In rostral gyrus white matter, the density of neuroblasts was not different from shams and the response was highly variable among injured piglets, ranging from increased neuroblast density adjacent to the lesion to a lower density than sham piglets. The density of $BrdU^+/DCX^+$ cells was greater in rostral gyrus white matter, but comprised only 1% of DCX^+ cells. Neuroblast density in the insular cortex was not different from shams, but was four-fold greater than the rostral gyrus, indicating that migration to this region may still be prioritized. In conclusion, we have observed a modest increase in neuroblast density in the injured rostral gyrus comprised of existing neuroblasts, which was highly variable. Future work will aim to determine the factors that result in targeting to the lesion vs. the potential re-routing of neuroblasts away from the lesion site and investigate the consequences of neuroblasts targeting white matter lesions, which may lead to further complications such as post-traumatic epilepsy. The immature piglet brain is a helpful model of children where response to injury is diverse and efforts to repair lesioned tissue may contribute to post-TBI sequelae.

Keywords: Pediatric TBI, Neurogenesis, Cortical Impact, Swine

A8-05

SPECIFIC MODES OF REMYELINATION ARE ASSOCIATED WITH IMPROVED BEHAVIORAL OUTCOMES AFTER CONTROLLED CORTICAL IMPACT

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Damaged white matter in rats does not remyelinate after mild controlled cortical impact (mCCI). Treatment with minocycline (MINO) plus N-acetylcysteine (NAC) or MINO alone did remyelinate white matter damaged by mCCI. Using specific antigenic markers, we examined the fate of oligodendrocytes and oligodendrocyte precursor cells (OPCs) in the corpus callosum at times of demyelination and remyelination. During demyelination in rats treated with MINO alone, resident oligodendrocytes became apoptotic and OPC number increased at the injury site. At times of remyelination, OPCs differentiated into myelinating oligodendrocytes. In contrast, during demyelination in rats treated with MINO plus NAC, resident oligodendrocytes were retained and OPC proliferation suppressed. These data suggest that remyelination was mediated by OPCs after treatment with MINO, but by resident oligodendrocytes after treatment with MINO plus NAC. Injured rats treated with NAC alone showed no signs of remyelination. These data strongly suggest that the differences between MINO- and MINO plus NAC-mediated remyelination resulted from drug synergy between MINO and NAC.

After mCCI, MINO plus NAC-treated rats have a better functional recovery than rats treated with MINO alone. Injured rats treated with MINO or NAC alone were unable to acquire a shock zone location during a spaced version of the active place avoidance task that utilized a 24-hour intertrial interval. In contrast, MINO plus NAC-treated rats both acquired and retained spaced active place avoidance. Acquisition of active place avoidance requires midline white matter tracts to function properly. Thus, the repair of white matter by MINO plus NAC may result in greater recovery of brain function following traumatic injury than seen with MINO alone.

Keywords: remyelination, repair, drug synergy, off label drug use, memory

A8-06

GOLLI-MYELIN BASIC PROTEIN IS REQUIRED FOR MATURATION OF OLIGODENDROCYTE PROGENITORS AND REMYELINATION OF CONTUSED SPINAL CORDS

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The Golli-Myelin Basic Protein (Golli-MBP) is a transcriptional chimera, consisting of 5′ Golli-specific, and shared 3′ MBP exons, whose exact function remains elusive. Quantitative RT-PCR confirmed that in M3 enhancer knock-out mice (M3KO), Golli-MBP RNA expression is reduced 5-fold, displaying no phenotypic abnormalities in developing nor adult mice. However, ES cells derived from M3KO, compared to wild-type (WT) mice, were unable to mature into oligodendrocyte progenitor cells (OPCs) in the presence of neither platelet-derived growth factor (PDGF) nor fibroblast growth factor (bFGF). To test for the physiological implications of OPC dismaturation, WT and M3KO mouse spinal cords were contused (90 kD force), and dissected from the animals for analysis. One week post-injury, M3KO spinal cords exhibited areas of continued demyelination and severely reduced remyelination, while remyelination in WT mice was more robust. Using Basso Mouse Scale hindlimb assessments, injured M3KO recovery was significantly lower and delayed, compared to WT up to 6 weeks ($p < 0.05$). Phospho-Receptor Tyrosine Kinase protein microarrays, probed using extractions from WT and M3KO spinal cords, showed that αPDGF and FGF3 receptor activation was reduced by 84.3% and 176%, respectively, in the M3KO mice at 24 hours. From these data, we hypothesized that spinal cord M3KO OPC proliferation and differentiation would also be retarded *in vivo* as compared to WT. Immunohistochemistry of WT and M3KO mouse spinal cords confirmed this. Staining for the proliferation marker, Ki67, showed that 12.4% of cells in WT spinal cords, 1 week post-injury at 1 mm rostral from the epicenter, were pro-proliferative, as compared to 4.7% in M3KO ($p < 0.009$). Additionally, there was a significant reduction of NG2+ OPCs in 1 week, post-contused spinal cords at 2 mm rostral (WT: 3728, M3KO: 1867, $p < 0.05$), 1 mm caudal (WT: 2472, M3KO: 1000, $p < 0.02$), and 2 mm caudal (WT: 2216, M3KO: 1173, $p < 0.004$). These data show that functional Golli-MBP is required for the rapid proliferation and differentiation of OPCs after contusional spinal cord injury.

Keywords: Remyelination, Golli-Myelin Basic Protein, Oligodendrocyte Progenitor, Cell Differentiation

A8-07

EXAMINING THE TIME-COURSE OF D-CYCLOSERINE ADMINISTRATION IN DEVELOPING RATS FOLLOWING LATERAL FLUID PERCUSSIVE INJURY

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This study examined the effects of D-cycloserine (DCS) administration on N-methyl-D-aspartate (NMDA) receptor mediated signaling in the subacute injury phase following severe lateral fluid percussive injury (LFPI) on postnatal day 19 (P19) rats. DCS is a partial agonist at the NMDAR glycine-binding site, and has been investigated as a potential therapeutic approach to cognitive dysfunction following TBI in the adult, but not the juvenile, rat. P19 rats underwent LFPI and received 5 DCS doses (30 mg/kg; 0.25 ml/kg) every 12 hours starting 24 hours post-injury,

or saline vehicle. Injured parietal cortex and underlying hippocampus were probed via western blotting on post-injury day (PID) 2, 4, and 14. We examined various markers of NMDAR mediated plasticity, including NR2A, NR2B, NR1, CaMKII, pCaMKII, CREB, and pCREB. This study is novel in charting the time-course of plasticity-related molecular changes after injury and with glutamatergic treatment. We found that reductions in NR2A (16% reduction in untreated injured vs. uninjured, $p < 0.1$) and pCaMKII (39% reduction in untreated injured vs. uninjured, $p < 0.05$) in the injured rat hippocampus on PID4 were alleviated following treatment with DCS. Further, NR2A expression in injured PID4 hippocampus was significantly higher in treated injured animals than in untreated injured animals at the $p < 0.1$ level. Injured rats treated with DCS have similar levels of NMDAR related molecular markers compared to uninjured, untreated controls (there were no significant differences between treated injured animals and controls in NMDAR related molecular expression). Early DCS treatment helps to alleviate some early deficits in NMDAR related signaling in injured hippocampus following severe lateral fluid percussive injury. Thus, DCS administration following pediatric TBI in the subacute phase represents a powerful potential target for early intervention. This research was supported by UCLA BIRC, NS027544, HD076418, and the Joseph Drown Foundation.

Keywords: Pediatric, D-Cycloserine, NMDAR, FPI, Severe FPI

A8-08

MIASCI ONLINE: AN ANNOTATION TOOL FOR THE MINIMAL INFORMATION ABOUT A SPINAL CORD INJURY EXPERIMENT (MIASCI) REPORTING STANDARD

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The lack of reproducibility in many areas of science, including spinal cord injury (SCI) research, results in increased operational costs and a decline in the productivity of research and development. Poor reproducibility is due in part to the lack of common reporting standards. To address this significant problem, over the past four years an *ad hoc* consortium of scientists has developed a minimal information reporting standard for SCI experiments, known as MIASCI. Our latest version of MIASCI captures information about 11 aspects of an SCI experiment: investigator, organism, surgery, perturbagen, cell transplantation, biomaterials, histology, immunohistochemistry, imaging, behavior, biochemistry, molecular biology, and data analysis and statistics. For each of these aspects, MIASCI enables scientists to capture essential metadata about the study design, materials and methods. Collecting all the information needed to comply with MIASCI is challenging and if an entirely manual entry approach is used, it is difficult to describe experimental workflows or study groups, and the relationships between them. Here, we present *MIASCI Online*, a web-based annotation tool that makes use of existing ontologies and addresses these problems. Importantly, MIASCI Online produces output that is both human readable and ready for deposit and analysis in data- and knowledgebases. Example queries supported by MIASCI Online will be illustrated and their role in facilitating scientific discovery discussed.

Acknowledgments

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Keywords: ontology, database, reporting standard, informatics, reproducibility

A8-09

IMMEDIATE AND PERSISTENT DENDRITIC HYPERTROPHY IN THE BASOLATERAL AMYGDALA FOLLOWING EXPERIMENTAL DIFFUSE TRAUMATIC BRAIN INJURY

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Increasing prevalence of traumatic brain injury (TBI) and comorbid anxiety disorders such as post-traumatic stress disorder (PTSD) warrants attention for better understanding of underlying pathomechanisms. The amygdala is involved in processing emotional and stressful stimuli and is implicated in anxiety disorders, like PTSD. The basolateral amygdala (BLA) receives rich inputs from sensory and limbic structures and modulates stress, fear, and emotional learning and memory. Structural plasticity within amygdala circuits may underlie emotional sequelae of TBI. The purpose of this study was to quantify temporal changes in dendritic complexity of excitatory neurons in the BLA after TBI. Adult male rats were subjected to a diffuse brain injury by midline fluid percussion or a sham injury. At post-injury days (PID) 1, 7 and 28, brain tissue from sham and brain-injured rats was processed for Golgi or silver stain, and analyzed to quantify BLA dendritic complexity in pyramidal and stellate neurons and regional neuropathology, respectively. Compared to sham, brain-injured rats at all PID investigated showed enhanced dendritic complexity proximal to the soma, and at later time points at distal portions in both BLA cell types as revealed by Sholl analysis. However, the BLA was spared from neuropathology demonstrated by limited argyrophilic accumulation at all time points measured, in contrast to other regions. These data suggest an immediate and chronic enhancement of dendritic complexity within the BLA after a single TBI, without neuropathology. Increased dendritic complexity would alter information processing into and through the amygdala, which may contribute to affective symptoms after TBI, and possibly the development of PTSD.

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Keywords: amygdala, structural plasticity, emotion, post traumatic stress disorder

A8-10

INDUCED MOTOR NEURON DIFFERENTIATION FROM ENDOGENOUS NEURAL STEM CELLS IN MICE AFTER SPINAL CORD INJURY

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Direct manipulation of endogenous neural stem cells (eNSCs) is an attractive strategy to repair damage and replenish cells lost after spinal cord injury (SCI). However, the gliogenic microenvironment drives differentiation of eNSCs towards astrocytes. Previously we guided human NSCs (hNSCs) to generate motor neurons (MNs) in vitro by regulating the PI3K or STAT3 signaling pathway. Here we ask whether a combination of PI3K and STAT3 would enhance MN differentiation and decrease gliogenesis in vitro and in vivo. Both hNSCs and mouse NSCs (mNSCs) generated more $HB9^+$ cells (a MN marker) after priming with FGF2 and PI3K/STAT3 inhibitors, as compared to controls. To model SCI in vitro, we performed a moderate stretch injury on hNSCs. The combination treatment with FGF2 and PI3K/STAT3 inhibitors greatly increased the number of $HB9^+$ cells, suggesting more MNs differentiated from hNSCs after injury in vitro. For in vivo studies, FGF2, Heparin and PI3K/ STAT3 inhibitors were intrathecally infused after contusion SCI. Such treatments dramatically increased NeuN and ChAT (another MN marker) expressing cells and decreased $GFAP^+$ cells 4-week post injury. More excitingly, the locomotor functional score in the FGF2/Heparin/ inhibitor group was significantly higher than in the control groups, accompanied by improved rearing times. In summary, MN differentiation from neural stem cells can be induced by FGF2 together with PI3K and STAT3 inhibitors both in vitro and in vivo. Our novel findings suggest that the gliogenic microenvironment after SCI can be manipulated to allow endogenous spinal cord NSCs to generate neurons instead of astrocytes, and therefore, eNSCs can be attractive candidates as an alternative to cell transplantation to facilitate neural repair after SCI.

Keywords: neural stem cell, motor neuron, signaling pathway, spinal cord injury

A8-11

INTERACTIVE ROLE OF MATRIX METALLOPROTEINASE 9 AND OSTEOPONTIN IN OLFACTORY BULB SYNAPTOGENESIS FOLLOWING TBI

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Traumatic brain injury (TBI) produces diffuse axotomy and synaptic disruption, causing a variety of functional deficits. Axons of olfactory receptor neurons (ORNs), which transmit sensory signals through the cribriform plate, are particularly vulnerable to injury, resulting in deafferentation of olfactory bulb (OB) glomeruli. Normally, ORN turnover produces continuous axon regeneration and reinnervation of the OB. After trauma, this process becomes aberrant, often producing persistent anosmia. Although the mechanism of OB synaptogenesis is not understood, prior studies suggest matrix metalloproteinases (MMPs) regulate OB synaptic repair after injury. MMP9 elevation/activity is documented at sub-acute post-injury intervals, but its role in OB synaptogenesis remains unclear. Recently, we posited that post-injury elevation of cytokine osteopontin (OPN), an MMP substrate, represents a novel mechanism for MMP9-mediated synaptic recovery. MMP cleaved OPN binds integrin receptors, promoting glial proliferation and migration, as well as cytokine and growth factor production for synaptogenesis. Here we assessed MMP/OPN interaction in WT and MMP9 KO mouse OB during acute (1d, 3d), degenerative (7d), and early regenerative (21d) intervals. We hypothesized that, after central fluid percussion TBI, time-dependent changes in MMP9 activity alter OPN fragment generation, signaling neuroglial activation to promote OB synaptogenesis. Zymographic analysis showed $\sim$3 fold increase in MMP9 activity at 7d. Western blot (WB) probe confirmed this increase was accompanied by 7d elevation of 47kD OPN integrin binding fragment. By 21d, MMP9 activity and OPN fragment production were below controls. With MMP9 KO, 47kD OPN expression at 7 and 21d was attenuated, supporting MMP9 role in OB OPN processing after TBI. Further, OB ultrastructure at 7d post-injury showed disrupted synaptic organization, an effect exacerbated by MMP9 KO. Subsequent WB showed no OB change in the common pre-synaptic marker Synapsin-I, however, ORN-specific olfactory marker protein (OMP) was reduced at 3d, returning to control level by 21d. Notably, MMP9 KO prolonged OMP reduction beyond 7d, likely interfering with ORN reinnervation. Collectively, these results support MMP9/OPN interaction and OPN fragment signaling during OB reactive synaptogenesis, particularly with regard to TBI-induced reinnervation of deafferented glomeruli.

Support: NIH-NS056247, NS057758
Keywords: MMP9, Osteopontin, Synaptogenesis, Olfactory Bulb

A8-12

THE EFFECT OF MILD TRAUMATIC BRAIN INJURY (MTBI) ON THE STRUCTURAL PLASTICITY OF THE AXON INITIAL SEGMENT (AIS)

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The AIS is the site of action potential (AP) initiation, thereby a crucial regulator of neural activity. Located on the proximal axon near the soma, the precise position and length of the AIS varies with neuronal subtypes. Ankyrin-G is the master structural protein regulating neuron excitability via clustering voltage-gated sodium channels (NaV). In pyramidal neurons, the high-density of NaV1.6 at the distal AIS sets the threshold for AP generation. It has been shown that AIS modification alters neuronal excitability following deafferentation of neural circuits. Recently, in mTBI-mice, we have demonstrated dramatic alterations in the electrophysiological status of intact neocortical pyramidal neurons, consistent with AIS-specific changes, as well as the circuit disruption associated with mTBI. Since AIS architecture modulates neuronal excitability, the purpose of the current study was to determine if mTBI induces AIS structural plasticity within a well-defined subset of intact neocortical pyramidal neurons. Thy1-YFP mice exposed to either sham or mild central fluid percussion injury were perfused after a 2-day recovery period. Antibodies to ankyrin-G and NaV1.6 were used to fluorescently label the AIS. Confocal microscopy was employed to identify intact YFP^+ pyramidal neurons in layer 5 of S1 barrel field, whose axons were continuous from the soma of origin to the subcortical white matter. Immunofluorescent profiles of ankyrin-G or NaV1.6 were then superimposed on the YFP^+ axonal traces to determine the start position with respect to the somas of origin, and length. Alteration of these parameters was interpreted as to reflect AIS structural plasticity. We found that while mTBI had no effect on ankyrin-G start position, the length was significantly reduced. This demonstrates a shortening of the AIS from the distal end, where we also observed a peak in NaV1.6 immunofluorescent signal, consistent with the site of AP initiation. This change in AIS structure most likely explains some of the electrophysiological abnormalities seen within the intact neocortical pyramidal neuron population after mTBI.

Keywords: Mild Traumatic Brain Injury, Transgenic Mouse Model, Plasticity, Axon Initial Segment, Ankyrin-G, Voltage-Gated Sodium Channel

B1 Poster Session III - Group B: Aging

B1-01

DECOMPRESSIVE CRANIECTOMY IN CONJUNCTION WITH LESION EVACUATION IN GERIATRIC TRAUMATIC BRAIN INJURY: A PROPENSITY SCORE ANALYSIS

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When it comes to evacuating intracranial hemorrhagic lesions in patients with traumatic brain injury (TBI), neurosurgeons perform either a craniotomy or a decompressive craniectomy (DC). The aim of the present study was to estimate the impact of DC on outcomes in elderly patients. This retrospective cohort study, conducted in an institute that specializes in neurosurgery in Japan from April 2009 to June 2014, included 91 consecutive patients with TBI (aged 60 years or over) who underwent evacuation of intracranial hemorrhagic lesions. Patients were divided into two groups: craniotomy only or DC. We set the primary endpoint as an unfavorable outcome (death or vegetative state), as evaluated on the Glasgow Outcome Scale at 6 months after injury. The secondary endpoints included existence of delayed hemorrhage and occurrence of hydrocephalus requiring shunt placement. The inverse probability of treatment weighting (IPTW) method was used to develop a propensity model to adjust for baseline imbalances between groups. The DC group exhibited greater severity both in clinical and computed tomography findings according to baseline characteristics. After adjusting for these differences by IPTW using the propensity score, DC was significantly associated with unfavorable outcomes (adjusted odds ratio [OR], 8.00; 95% confidential interval [CI], 2.30–27.84; $p = 0.002$) and delayed hemorrhage (adjusted OR, 13.42; 95% CI, 1.52–118.89; $p = 0.022$). There was no significant difference in the occurrence of hydrocephalus requiring shunt placement. Our study showed that DC in conjunction with evacuation of intracranial hemorrhagic lesions was associated with worse functional outcome in elderly patients with TBI.

Keywords: decompressive craniectomy, Glasgow outcome scale, delayed hemorrhage, elderly, propensity score, inverse probability of treatment weighting

B1-02

THE ROLE OF TAU AND OTHER PATHOLOGIES IN AN ANIMAL MODEL OF REPETITIVE MTBI

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The Chronic Effects of Neurotrauma Consortium or CENC is dedicated to understanding the chronic sequelae associated with neurotrauma, primarily focused on mild TBI (mTBI)/concussion incurred by U.S. service personnel. However, little is known about the timeline and sequence in which tau is processed following TBI, nor about the relationship with other TBI-dependent neuropathologies such as neuroinflammation and cerebrovascular changes. This study is evaluating tau alterations and accompanying neuropathologies over time after r-mTBI in hTau transgenic mice. hTau mice aged either 8–12 weeks will receive either r-mTBI or r-sham in order to control for effects of repeated anesthesia. Mice will be euthanized for neuropathological, genomic and biochemical analyses at 24 hrs, 5, 10 and 15 days, 3, 6 and 12 months after last mTBI/anesthesia. For the 15 day and 3, 6 and 12 month time points post injury mice will undergo a battery of neurobehavioral test in the 2 weeks immediately prior to euthanasia. The entire paradigm is being replicated in hTau mice aged 12 months at the time of injury, to study the effects of age at time of injury. r-mTBI in the young cohort shows learning impairment post injury that progressively worsens from 2 weeks to 12 months. To date, Tau IHC and ELISA results suggest that r-mTBI is associated with a transient injury dependent increase in p-tau accumulation with greater dendritic and membranous staining in the cerebral cortex beneath the impact site without neurofibrillary tangles. While a trend for an increase in aggregated tau at 12 months post injury was observed, r-mTBI was not associated with elevated brain levels of abnormal soluble tau phosphorylation. This study is ongoing and will take several years to complete; our previous data suggest that neuroinflammatory pathology is key in this model and that TBI-dependent tau pathology will be evident in the older mouse models where tau pathology already exists.

Keywords: Tau, repetitive mTBI, inflammation, animal model

B1-03

CHRONIC IMPAIRMENT OF CEREBRAL BLOOD FLOW IN A MOUSE MODEL OF REPETITIVE MILD TRAUMATIC BRAIN INJURY

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Repeated exposure to mild traumatic brain injury (mTBI), as seen in contact sports injuries, is known to predispose individuals to development of neurodegenerative diseases such as Alzheimer's Disease and Chronic Traumatic Encephalopathy (CTE). CTE is characterized by deposition and hyper-phosphorylation of the microtubule-associated protein tau throughout the brain. In addition to aberrant proteinopathy, neurodegenerative diseases are often associated with cerebrovascular abnormalities, including changes in cerebral blood flow (CBF), and loss of Blood Brain Barrier (BBB) integrity. Owing to the prevalence of mTBI, there is an urgent requirement for animal models recapitulating the pathological hallmarks, cognitive deficits, and cerebrovascular components of neurodegeneration following repetitive mild head trauma. We used heterozygous transgenic hTau mice expressing all 6 isoforms of human tau on a null murine tau background, allowing for a clinically relevant investigation of the effects of repetitive mTBI (r-mTBI) on cerebrovascular mechanics in the presence of human tau. The closed-head mTBI was administered to mice under isofluorane anesthetic using a 5 mm blunt metal impactor tip at a velocity of 5 m/s and a strike depth of 1 mm, positioned midway to the sagittal suture. We administered 2 hits every week for 3 months to replicate the incidence of mTBI that can occur over the course of a career in contact sports. We measured CBF in both hTau and wild-type mice 3 months and 7 months post-injury, respectively, using laser Doppler imaging. We observed a significant decrease in CBF in wild-type mice ($10.66\% \pm 1.44\%$ compared to sham) and hTau mice ($8.92\% \pm 1.39\%$ compared to sham) This effect of r-mTBI on CBF may provide rationale for the link between head trauma and the development of neurodegenerative disorders like CTE. We will continue to evaluate

the impact of r-mTBI on the cerebrovasculature by assessing BBB integrity and examining specific vascular markers at various time-points post-injury in upcoming studies.

Keywords: Animal Models, Cerebral Blood Flow, Laser Doppler Imaging, hTau Mice, Closed-Head Injury

B1-04

AGING RELATED DIFFERENCES IN PATTERNS OF MEDICATION USE AT TIME OF TRAUMATIC BRAIN INJURY

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Background/Purpose: The influence of comorbidities and medications on injury rates and recovery in older adults with traumatic brain injury (TBI) still remains largely unexplored. Elderly patients are often taking several prescriptions at the time of injury, and there may be correlations between the use of any number of medications and the incidence of TBI. This project seeks to determine patterns of prescription medication and supplement usage and among patients who have suffered a TBI.

Methods: This was secondary data analysis of an ongoing prospective cohort study (N = 297). Cohorts include older (55 years of age and above) and younger (<55) persons following mild TBI as well as both older and younger non-injured age and gender-matched controls. Medication use (to include both prescription and supplements) at time of injury were obtained from medical records and self-report. Medications were collapsed into 14 categories of common drug classifications (e.g., beta-blockers, diuretics, vitamins, etc). Descriptive statistics and chi-squared analyses were performed to determine cohort differences in medication use.

Results: Older adults were more likely to be on at least one medication at time of TBI (87%) than those in the younger injured cohort (55%). Older adults with TBI were also more likely to be on any medication than older adult controls (87 vs. 77%). Similar findings were seen in younger TBI (55%) versus younger non-injured controls (48%). The most common types of medications used in persons with mild TBI were statins, aspirin and ACE inhibitors.

Conclusions: This research has important implications for improved injury prevention-related education of patients using these medications. The increased drug usage, particularly those with vasoactive properties, by the elderly places them at greater risk of injury and close monitoring is warranted when prescribing or adjusting these medications.

Supported by NIH/NINDS R01NS077913

Keywords: medication; supplements; injury prevention

B1-05

AGING RATS SHOW ALTERATIONS TO GLIAL CELL ACTIVATION AND FUNCTIONAL RECOVERY AFTER SPINAL CORD INJURY

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Spinal cord injury (SCI) among the aging population has been steadily increasing since the 1980's and is associated with high rates of comorbidities and delayed recovery. Increases in oxidative stress and reactive oxygen species in aging tissue are suggested to increase the activation of glial cells and lead to chronic inflammation, which may contribute to the delayed recovery to SCI seen in the aging population. This study aimed to determine the effect of age on glial cell activation both basally and after SCI, and determine functional outcomes after injury with aging. Briefly, young (3 months old) and aged (12 months old) male rats were sacrificed and tissue was processed for histology to determine basal glial activation states. Histology revealed increased staining of markers for microglia (Iba1, $p = 0.0456$) and astrocytes (GFAP, $p = 0.0199$) in naïve tissue of aged animals compared to young animals. To investigate locomotor function after injury, a second group of young and aged male rats were subjected to a moderate contusion SCI before being assessed through a locomotor battery. Locomotor function was assessed once a week for 28 days using the Basso, Beattie, and Breshnahan (BBB) scale, the ladder walk, and footprint analysis. Functional analysis revealed that compared with young animals, aged animals showed significantly reduced general motor function at 7 dpi ($p < 0.001$), significantly decreased toe spread ($p = 0.0231$) and stride length ($p = 0.0238$) at 28 dpi, and a trend toward reduced performance on the ladder task at both 14 and 28 dpi. These results demonstrate that aged rats demonstrate increased basal glial activation and a worsened functional outcome to injury, findings that are essential towards elucidating the mechanisms of age-related differences in response to SCI.

Keywords: oxidative stress, microglia, astrocyte, functional recovery

B1-06

1H-MRS SUGGESTS MECHANISMS UNDERLYING POOR RECOVERY AFTER INJURY TO THE AGED BRAIN

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Traumatic brain injury (TBI) has an especially large impact on individuals over the age of 65, who are more likely to be hospitalized, and have higher mortality and poorer outcomes than younger adults. However, the reasons for this discrepancy remain poorly understood. We used non-invasive proton magnetic resonance spectroscopy (^{1}H-MRS) to explore potential biological mechanisms in the aged brain that may account for the poor recovery in older individuals with TBI. ^{1}H-MRS is a neuroimaging technique that measures neurochemicals (biomarkers) that reflect specific aspects of brain function, for example, neuronal mitochondrial status (N-acetylaspartate), oxidative stress (glutathione and ascorbate), neurotransmission (glutamate, aspartate, GABA), and edema (taurine, *myo*-inositol). We administered TBI by controlled cortical impact to the right sensorimotor cortex (2 mm depth, 3.5 m/s, 300 ms) in young adult (3 month) and aged (20–22 month) male rats. A Varian 9.4 Tesla system was used to collect water-suppressed MR spectra ($TE = 2$ ms, $TR = 4000$ ms) from the ipsilateral hippocampus before TBI, and after TBI at 1 hour and 1, 3, 7, 14, and 28 days. Sensorimotor function was measured with the beam walk task over the same time course. We found that functional impairment was significantly worse in the aged rats after TBI, reflecting the poorer outcomes seen in older human survivors of TBI. ^{1}H-MRS biomarker changes after injury were also more severe in the aged rats, including a larger decrease in N-acetylaspartate, phosphocreatine, and taurine, and a more prolonged decrease in glutamate compared with younger adults. Our results indicate greater metabolic disturbances in the aged injured brain, particularly in markers of bioenergetic impairment (n-acetylaspartate, phosphocreatine), excitotoxicity (glutamate), and edema

(taurine). These age-related differences in the cascade of cellular injury mechanisms may contribute to the poor functional recovery of aged rats after TBI. Our findings point to bioenergetic impairment, excitotoxicity, and edema as potential therapeutic targets for improving recovery after TBI in older individuals.

Keywords: Aging, Traumatic Brain Injury, Magnetic Resonance Spectroscopy, Imaging, Biomarker, Secondary Injury

B1-07

EFFECT OF AGING ON HIPPOCAMPAL-DEPENDENT COGNITION AND NEUROINFLAMMATORY RESPONSES AFTER TRAUMATIC BRAIN INJURY

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Traumatic Brain Injury (TBI) is a powerful environmental risk factor for the development of Alzheimer's disease and dementia. Age is a significant factor in both the risk and incidence of acquired brain injury. TBI recovery and outcomes are worse in elderly patients with higher fatality rates and greater severity of TBI-related disabilities. In animal models recapitulating TBI, aging predisposes increases in neuronal loss, inflammation, and motor dysfunction shortly after injury. However, long-term cognitive outcomes of TBI in aging animals and underlying mechanisms for age-related exacerbation of TBI have not yet been investigated. In the current study, we characterized the effect of aging on long-term cognitive deficits after TBI and on injury-induced neuroinflammatory responses. TBI was generated through controlled cortical impact over the right parietal cortex in 3 and 22–24 month old male mice. Thirty days after injury, hippocampal-dependent learning and memory functions were measured using the radial arm water maze (RAWM), novel object recognition (NOR), and contextual fear conditioning (CFC) assays. Our data demonstrates that both age and TBI negatively affects hippocampal-dependent learning and memory. Furthermore, aging worsens TBI-induced hippocampal-dependent memory impairments in particular.

While aging increases both pro- and anti-inflammatory responses in many inflammatory contexts, it is unclear if aging upregulates and maintains pro-inflammatory responses or results in diminished anti-inflammatory responses after TBI. We characterized the inflammatory responses of the injured brains of young and old animals by quantitative PCR at acute and sub-chronic time points after a TBI. Our results demonstrate that 24 hours post-injury, there was increased inflammatory responses in old animals. At 7 days after injury, there was a significant decrease in anti-inflammatory responses in old animals compared to the young. This suggests an imbalance in the regulation of inflammation in the aging brain which may sustain a pro-inflammatory environment after injury.

Keywords: Hippocampal-dependent memory, Novel Object Recognition, CCI, Mice, Neuroinflammation

B1-08

MW151, A SMALL MOLECULE INHIBITOR OF NEUROINFLAMMATION, PREVENTS CLOSED HEAD INJURY INDUCED COGNITIVE DEFICITS IN APP/PS1 KI MICE

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Epidemiological studies have associated increased risk of Alzheimer's disease (AD) related clinical symptoms with a medical history of head injury. Currently, little is known about pathophysiology mechanisms linked to this association. Persistent neuroinflammation is one outcome observed in patients after a single head injury. Neuroinflammation is also present early in relevant brain regions during AD pathology progression. In addition, previous mechanistic studies in animal models of either traumatic brain injury or AD link neuroinflammation as a contributor to neuropathology and cognitive impairment seen in each respective model. This raises the possibility that selective targeting of the dysregulated cytokine response, a component of the neuroinflammation that contributes to neuronal dysfunction, may be a useful therapeutic approach. MW01-2-151WH (MW151) is a novel, CNS-penetrant small molecule drug that selectively restores injury- or disease-induced overproduction of proinflammatory cytokines towards homeostasis. We have previously reported that MW151 administered post injury is efficacious in a closed head injury (CHI) model of diffuse TBI in mice. Therefore, we explored the potential interplay of neuroinflammatory responses in TBI and AD by intervention with MW151 to attenuate the dysregulated proinflammatory cytokine response seen in APP/PS1 knock-in (KI) mice following a CHI. Based on prior work, showing a delayed peak neuroinflammatory response at 7 days post injury (p.i), mice received treatment every other day from day 7-to-27 p.i. In radial arm water maze (RAWM) testing (day 29 and 30 p.i.), the APP/PS1 KI mice + CHI + MW151 made significantly fewer errors than the APP/PS1 KI mice + CHI + vehicle. Consistent with a link between neuroinflammatory responses and altered risk for AD-associated pathology changes with head injury, our results show that intervention with a small molecule experimental therapeutic (MW151) which selectively attenuates proinflammatory cytokine production can improve cognitive behavior outcomes.

Keywords: neuroinflammation, cytokines, astrocytes, microglia, amyloid plaque

B1-09

WHO GETS HEAD TRAUMA OR RECRUITED IN MILD TRAUMATIC BRAIN INJURY RESEARCH?

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Background: Outcome from mild TBI is heterogeneous in part due to pre-injury individual differences that typically are not well described or understood. Our objective was to provide a comprehensive description of the pre-injury health characteristics of a cohort of patients who sustain head trauma and undergo evaluation in an emergency department. The number of people with specific pre-injury health problems, singly and in combination, was determined.

Methods: Pre-injury health characteristics of all consecutive patients (N = 3,023; average age = 55.0 years, SD = 24.0; male = 56.4%) who underwent head CT due to acute head trauma in the emergency department of Tampere University Hospital, Finland between August 2010 and July 2012 were examined. Patients were screened to obtain a sample of working aged adults with no pre-injury medical or mental

health problems who had sustained a ''pure'' MTBI. Of all patients screened, 1,970 (65.2%) had a MTBI, 370 (12.2%) had a more severe TBI, and 683 (22.6%) had a head trauma without signs of brain injury. Injury-related and participant-related data were collected from hospital records. We investigated the frequency of pre-injury diseases and conditions in the population and the effect of applying different inclusion/exclusion criteria on patient enrollment.

Results: The most common pre-injury diseases were circulatory (39.4–47.0%), neurological (23.7–28.4%), and psychiatric (25.8–27.7%) disorders. Alcohol abuse was present in 18.4–24.3%. The most common medications were for cardiovascular (34.8–36.9%), central nervous system (27.7–30.9%), and blood clotting and anemia indications (21.5–24.6%). Of the screened patients, only 2.1% met all the enrollment criteria. Age, neurological and psychiatric problems were the most common reasons for exclusion.

Conclusions: Most of the MTBI patients have some pre-injury conditions or regular medication that could influence clinical outcome. Excluding patients with pre-existing conditions creates a significant selection bias.

Keywords: mild traumatic brain injury, comorbidity, patient recruitment, CT imaging

B2 Poster Session III - Group B: Neurodegeneration

B2-01

THE ROLE OF APOPTOSIS IN LONG-TERM AXONAL, MICROVASCULAR AND BLOOD-BRAIN BARRIER DAMAGE AFTER TRAUMATIC BRAIN INJURY IN RATS

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Introduction: Acute and long-term disabilities associated with TBI are mediated by multiple molecular and cellular pathobiological cascades initiated by the acute traumatic event that potentially may lead to chronic traumatic encephalopathy (CTE), Alzheimer's disease (AD) and other dementias. Data indicate that AD is associated with caspase 3-mediated apoptosis, tau pathologies and abnormal angiogenesis. The goal of this study is to evaluate microvascular abnormalities at acute and chronic stages following TBI in rats.

Methods: TBI in adult rats was induced by controlled cortical impact (CCI). Brain pathology was assessed at different time points from 24h to 3 months following injury using immunohistochemistry (IHC) on paraffin-embedded 6 μm brain sections and examined for the following biomarkers: cleaved caspase-3 (apoptosis), caspase cleaved tau (truncated at Asp421) (neuronal cytoskeleton damage), SMI-71 (blood-brain barrier) and CD34 (endothelial and progenitor cells) and CD68 (macrophages).

Results: TBI resulted in increased level of cleaved caspase-3 in both white and gray matter at the latest stages following injury. IHC staining of cleaved caspase-3 was gradually increased over the 3 month duration of the study in the corpus callosum and thalamus. These increased levels of caspase-3 were associated with an increase in the levels of microvascular, inflammatory and axonal damage markers predominantly in white matter. In corpus callosum, IHC with CD34 revealed TBI-induced microvascular abnormalities which were characterized by proliferation, irregular capillary formation and atypical structure of the new vessels. Further, increased perivascular accumulation levels of caspase cleaved Tau was observed at 2 and 3 month after injury. In addition, fluorescent co-staining experiments demonstrated co-localization of caspase-3 with SMI-71, and cleaved caspase-3 with CD68 suggesting involvement of apoptosis and delayed neuroinflammation in the mechanisms of miscrovascular damage in corpus callosum.

Conclusions: This study, for the first time, indicate that evolving white and gray matter degeneration following experimental TBI is associated with significantly delayed microvascular damage, abnormal angiogenesis and perivascular Tau accumulation. Our results suggest mechanisms underlying delayed apoptosis following TBI which could provide novel insights into chronic pathological responses to TBI and potential common mechanisms underlying TBI and neurodegenerative diseases.

Keywords: Cleaved caspase-3, chronic TBI, caspase cleaved Tau, blood-brain barrier, CD34

B2-02

THE ROLE OF TREM2 IN TRAUMATIC BRAIN INJURY-INDUCED NEUROINFLAMMATION AND NEURODEGENERATION

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Traumatic brain injury (TBI) affects approximately 3.8 million people annually and costs the US $48 million (NINDS). There is increasing evidence that individuals exposed to TBI, have increased risk of the development of multiple neurodegenerative conditions, including Alzheimer Disease (AD), Frontotemporal dementia, and chronic traumatic encephalopathy (CTE). TBI triggers a potent neuroinflammatory response characterized by astrogliosis, activation of microglia, infiltration of peripheral monocytes, and increased synthesis and release of pro- and anti-inflammatory molecules. Recent evidence suggests that alterations in innate immunity may promote neurodegeneration. This includes genetic studies demonstrating that heterozygous loss of function mutations in *Triggering Receptor Expressed on Myeloid cells 2 (TREM2)* is associated with a 3–4 fold higher risk for not only AD but multiple other neurodegenerative diseases similarly to TBI. TREM2 is a transmembrane receptor expressed on innate immune cells that has canonically been shown to negatively regulate Toll- Like receptor (TLR) signaling, a major pathway in innate immunity and inflammation. *The hypothesis of the current studies is that TREM2 deficiency will increase neuroinflammation and neurodegeneration following TBI and lead to long-term cognitive deficits*. Currently, no work has been published on the role of TREM2 in TBI. To examine the role of TREM2 in TBI-induced neuroinflammation and neurodegeneration, control mice were exposed to experimental TBI and examined at early time points. Notably, there was a substantial increase in TREM2+ cells in close proximity to the injury cavity and increased expression of TREM2 transcripts. TREM2 deficient mice were then given TBI and Immunohistochemistry as well as biochemistry was performed. These mice showed an altered inflammatory response. Lastly, motor and cognitive behavioral test were preformed on these mice. Though there are no motor deficits in these mice, there seems to be a deficiency in performing other cognitive tests. Mice are currently being aged to look at long-term aspects of TBI on TREM2 deficiency.

Keywords: TREM2, Macrophages, Transgenic mice, Alzheimer's Disease

B2-03

PROGRESSIVE LIMBIC ANTEROGRADE TRANS-NEURONAL DEGENERATION (LATND): A NEUROPATHOLOGICAL BIOMARKER IN TBI-INDUCED CTE & DEMENTIA

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Intro: In 1977, Torch et al. (NEUROLOGY 27:1157) described LATND in a 64 y.o. man who died after an 8-yr history of progressive behavioral-cognitive encephalopathy associated with sleep & autonomic disturbance, memory loss, dementia, & left temporal EEG slowing. At autopsy a large old left hippocampal cystic infarct was noted with atrophy of the ipsilateral 1) fimbria/fornix [Fx], 2) mammilary body [MB] & hypothalamus [HT], 3) mammillothalamic tract [MTT], anterior thalamus [AT], and 4) cingulum (Papez Circuit). Clinical decline was attributed to 1^o, 2^o & 3^o LATND. To determine its prevalence in adult & childhood, 128 published autopsy cases of hippocampal injury in 4 major categories were reviewed: Group A) stroke [49 cases]; Group B) TBI/surgical [24 cases]; Group C) encephalitis [41 cases]; Group D) kernicturus [14 cases]. 24 additional cases included: E) hippocampal sclerosis with TLE; F) neoplasm & carcinomatous-vasculitis; G) hyperinsulin-induced hypoglycemia; H) neurodegenerative child- & adult-onset Atypical & Familial Alzheimer's Disease, and Dementia Infantilis with schizophrenic-autistic features.

Methodology: Etiology, rate & degree of LATND, using a graduated scale of microscopic to grossly visible atrophy, was tabulated with symptomatology, as a function of survival time (ST, the period time from symptom-onset to death).

Results: Uni- and/or bilateral 1^o- 3^o LATND was observed following uni- or bilateral: A) hippocampal stroke [14L:14R:12L/R]; B) progressive boxing-induced TBI/CTE (dementia-pugilistica) & temporal lobe surgery/fornicotomy [1L:5R:18L/R]; C) limbic enchephalitis & carcinomatous vasculits [3L:1R:37L/R]; D) kernicterus/hypoxemia [14L/R]. Limbic degeneration was identified in 65% of stroke-, 75% of TBI-, 37% of encephalitis-, and 21% of kernicterus-affected hemispheres [a total of 194 hemispheres]. Average age of symptom-onset was: infarction, 59y; TBI, 38y; encephalitis, 36y; kernicterus, 2.5d. In most cases the extent & degree of symetrical or asymetrical LATND was linearly related to ST. In stroke, rate of progression was: Fx, 4 mos; MB, 6–8 mos; HT, 1.5 yr; MTT-AT, 3y 8 mos-5 yrs; in TBI: Fx, 4–5 mos; MB, 1–2.5 yr; HT, 5–11 yr; MTT-AT, 12–15 yrs. Rates of LATND progressed in the order: encephalitis > kernicterus > stroke > TBI, where mean ST was: kernicterus (2y), encephallitis (3.4y), infarction (3.9y), TBI (13.3y). Memory loss was most common in left or bilateral stroke, with apathy or emotional mood-related agitation & lability occurring in early LATND, with hallucinatory, paranoid, psychotic schizophrenic behavior & dementia 2–4 yrs later associated with degeneration of the anterior thalamus. TBI-dementia was seen after 5–10 y; encephalitic-dementia, after 3 mos-2y; kernicterus-related retardation after 1.5–2 y, also correlating with advancing anterior thalamic diencephalic degeneration.

Conclusion: LATND is commonly over-looked because of inadequate brain-sectioning & microscopic inspection, or lack of awareness of the process. LATND may account for early ''positive'' & later ''negative'' symptoms, as in ''burned-out'' stages of schizophrenia (e.g., dementia praecox), where early symptoms reflect hippocampal-diencephalic deafferentation, denervation-hypesensitivity or dysinhibition, followed by progressive LATND.

Future Research: Literature review of high-resolution CT, MRI, DTI, fMRI, PET, SPECT, MEG studies performed to-date, demonstrates that LATND may be a valid radiological biomarker in various hippocampal-sensitive conditions (e.g., AD, FTL/tau/prion & other human dementias, sports & military-related TBI/CTE, hypoxemia, hypo-glycemia, vasculitis, physical abuse/neglect with secondary cortisol/stress-induced PTSD). LATND, as a human & animal bio-model, holds future research promise in developing novel pharmacological and neuro-protective strategies for its prevention or reversal, including better helmet design for contact sports (e.g., boxing, football).

Keywords: Traumatic Brain and Other Hippocampal Injury, Hippocampal-Limbic Trans-neuronal Degeneration, Progressive Cognitive Dementia, Chronic Traumatic Encephalopathy, Traumatic and other Hippocampal Injury

B2-04

EMERGING ROLE OF GAPDH IN TBI INDUCED AMYLOIDOSIS

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TBI is a risk factor for developing Alzheimer's disease (AD), but TBI-induced mechanisms initiating AD are unknown and controversial. Oxidative stress (ROS) plays a role in AD and TBI. Many critical proteins are susceptible to oxidative modification, including GAPDH. It's known for its role as a redox-sensitive enzyme in glycolysis. However, it's a multifunctional protein involved in several cellular pathways. Injury or disease induced post-translational modifications alter its structure and activity allowing it to perform new and likely aberrant roles. These pathologic functions are not understood in disease generation or progression. In AD models, GADPH binds with beta-amyloid precursor protein (BAPP) and amyloid beta (AB) and is found in plaques, suggesting a role in amyloidosis, yet it's not known where in the pathway it acts. We hypothesize oxidative modification of GADPH facilitates translocation to and binding of BAPP and AB formation. Contusion-injured PND35 male rats were fed standard (STD) or ketogenic diet (KD). Ipsilateral cortex was isolated at 1, 3, 6 and 24 hrs post-injury and the following were quantified: GAPDH S-nitrosylation (GAPDH-SNO), coimmunoprecipitation of GAPDH, BAPP and AB, and cytosolic AB. STD animals show peak GAPDH-SNO at 1 hr followed by increased interaction between GAPDH and BAPP by 3 hrs. As interaction between GAPDH and BAPP decreased, those between GAPDH and AB increased in tandem with cytosolic AB. By 6 hrs, KD decreased production of AB. At 24 hrs, KD prevented increased interaction between both GAPDH, BAPP and AB. This is the first study to show GAPDH is involved in the immediate molecular cascade of events that may trigger AD. Once bound to BAPP, GAPDH may recruit or activate γ-secretase. GAPDH may facilitate AB plaque formation as it can dimerize and form aggregates similar to AB. If these events are regulated by ROS generation, it would be expected to see inhibition of this pathway with antioxidant administration. Our study is limited by KD ad-lib feeding which takes several hours for ketones to reach the brain. This is seen at 6 hrs, where little effect of KD was shown compared to 24 hrs. Future studies utilizing intravenous administration of ketones would resolve this. In summary, this study highlights the need to maintain redox balance post-injury as pathological amounts of ROS induce pathological signaling pathways.

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Keywords: traumatic brain injury, GAPDH, amyloid beta, Alzheimer's Disease, oxidative stress

B2-05

HIPPOCAMPAL DEGENERATION AFTER TRAUMATIC BRAIN INJURY: THE ROLES OF THE PGE2 EP1 RECEPTOR

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Over the past decade, PGE2 EP1 receptor blockers have been studied as a promising strategy for the treatment of neurological disorders and as a potential safer alternative to the cyclooxygenase-2 inhibitors. Preclinical data have demonstrated their efficacy in the treatment of ischemic and excitotoxic conditions by improving behavioral and

anatomical outcomes and by promoting cell survival. However, according to recent reports, the EP1 receptor roles are complex and the neuroprotective effects of its inhibition might be compensated or overpowered by adverse effects or toxicity in models of brain trauma and intracerebral hemorrhage. Consequently, the goal of this study was to investigate the effect of a selective EP1 receptor antagonist, SC-51089, on delayed neurodegeneration induced by traumatic brain injury (TBI) using a controlled-cortical impact (CCI) model with two different injury magnitudes in mice. The data demonstrate that neurological deficit scores at 24 and 48 h after CCI rose with increasing injury magnitude. Repeated post-treatment with 20 μg/kg of SC-51089 has no significant effects on neurological deficit scores as compared to vehicle groups with either magnitude. Of interest, ten days after the severe CCI in the SC-51089 treatment group, the delayed hippocampal tissue loss was greater as compared to controls. The data, in combination with published reports, suggest that the EP1 inhibition worsened delayed degenerative processes in the hippocampus at subacute time points after TBI, and that this effect is more profound with increased trauma severity, likely due to the increased contribution of hemorrhagic injury.

Keywords: controlled-cortical impact, Prostaglandin E2, Inflammation, G-protein coupled receptors

B2-06

REGIONAL EXPRESSION OF WILD-TYPE ALPHA-SYNUCLEIN AFTER TRAUMATIC BRAIN INJURY IN RATS

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Introduction: Synucleins (Syn), a family of synaptic proteins, includes alpha-synuclein (α-Syn), which plays a pivotal role in neurodegenerative diseases. The native function of α-synuclein is not completely understood, but is thought to involve regulation of synaptic vesicle trafficking. While the pathological forms of α-syn are considered to be the primary targets of TBI-associated neurodegeneration, disruption of the native function of α-Syn may contribute to pathology by diminishing synaptic function. The goal of the project was to examine the regional effects of TBI produced on wild-type α-Syn expression at 6 hours to 8 weeks post injury.

Methods: Male Sprague-Dawley rats were anesthetized and surgically prepared for controlled cortical impact (CCI) injury (4 m/sec, 2.6 mm) or sham surgery. Semi-quantitative Western blot measurements of the hippocampal, frontal cortex and striatal tissues from rats sacrificed at 6 h, 1 d, 1 wk, 2 wks, 4 wks and 8 wks after injury or sham operation (N = 6 per group).

Results: The expression of α-Syn was decreased ipsilaterally from 6 hrs to 8 wks in the hippocampus, at 1 wk and 2 wks in the frontal cortex, and bilaterally at 6 hrs only in the striatum ($P < 0.05$). Double-label immunofluorescent staining sacrificed at 1 wk after TBI or sham for α-Syn, neuron marker NeuN and astrocytes marker glial fibrillary acidic protein (GFAP) confirmed the Western blot findings. There is no overt change of NeuN immunostaining in regions of α-Syn loss. The increased expression of GFAP represents concomitant astrogliosis.

Conclusion: This study suggests that the decreased wild-type α-Syn expression in different brain regions after TBI may represent the complicity of α-Syn functions in the brain regions. Additional work is required to determine if this represents a shift toward more cytotoxic forms of α-Syn or a reorganization of synaptic vesicle trafficking after TBI.

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Keywords: traumatic brain injury, alpha-synuclein, Western blot, immunofluorescence

B2-07

NEUROPROTECTIVE EFFECT OF METHYLENE BLUE IN MODERATE TRAUMATIC BRAIN INJURY

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Methylene blue (MB) has unique energy-enhancing and antioxidant properties and has positive acute therapeutic effects following TBI in rats. We hypothesized that MB treatment would reduce lesion volume and improve functional recovery in a rat TBI model. Anesthetized rats underwent a 6 mm craniotomy over the left primary motor/somatosensory cortex region to expose the dura matter and were impacted using a pneumatic cortical impactor (impact velocity 5.0 m/s, 250 μs dwell time, and 1 mm depth) to mimic a moderate TBI. One hour or twenty-four hours after TBI, animals received intravenous infusion of saline (vehicle) or MB (1 mg/kg). MRI was utilized to longitudinally monitor T2 on days 0, 2, 7, and 14 after TBI. Comparisons were made with the progression of lesion volume, behavioral analysis (day 0, 2 7, and 14), and histology (day 14). Vehicle-treated animals initial lesion volume grew larger by 92% and peaked in size on day 2. By contrast, the acute and delayed MB-treated groups lesion volume growth was smaller on day 2 compared to the vehicle-treated group by 21% and 23%, respectively. Lesion volume in MB treated rats continued to significantly decrease in lesion volume compared to vehicle-treated rats on day 7 and 14 post-injury. Immunohistochemistry confirmed final lesion volumes upon sacrifice on day 14. The behavioral tests demonstrated impairment of motor function of vehicle- and MB-treated rats on day 0 and 2. However, MB treated rats demonstrated improved motor function by day 7, indicative of improved neurological status. MB markedly reduces lesion size and improves behavioral outcome even when delivered 24 hours post TBI. Delayed treatment would enable increased therapeutic benefits to larger patient population. These results suggest that restoration of mitochondrial function and minimizing reactive oxygen species production is a promising neuroprotective strategy in TBI.

Keywords: Traumatic Brain Injury, Methylene Blue, MRI, Behavioral analysis, Immunohistology

B2-08

TOXIC TAU SEEDS DERIVED FROM TRAUMATIC BRAIN INJURY MODELS ACCELERATE COGNITIVE DYSFUNCTION IN TAUOPATHY MICE

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The aggregation of tau protein into neurofibrillary tangles (NFTs) in the brain is a pathological feature of numerous neurodegenerative

disorders, as well as Traumatic Brain Injury (TBI). TBI induces cognitive changes affecting millions of people, as well as increased incidence of age-related neurodegeneration. Evidence from our lab and others suggests tau that forms on route to NFT formation—oligomers—are the most toxic tau species. We have shown increased levels of tau oligomers in neurodegenerative disease brains, as well as in TBI models. Using immunoprecipitation, we isolated tau oligomers from controlled cortical impact injured mice, fluid percussion injured and blast injured rat brains. Oligomers were characterized biochemically and by atomic force microscopy and were injected bilaterally in the hippocampi of mice overexpressing human tau (Htau mice). Mice were cognitively evaluated using novel object recognition and Y-maze tasks and brains were collected following testing. We found that tau oligomers form as a result of brain injury in three different rodent models of TBI and accelerated the onset of cognitive deficits, absent increased levels of cell death, in Htau mice. As we have seen previously in other diseases, oligomers collected from TBI can seed the aggregation of tau monomer *in vitro*. Moreover, mice injected with oligomers exhibited elevated levels of oligomeric tau in multiple brain regions, supporting the prion-like seeding and propagation capability of TBI-derived oligomeric tau. Our results suggest that tau oligomers play an important role in the toxicity underlying TBI, making them a viable therapeutic target for TBI and in preventing the increased acquisition of neurodegenerative disease later in life. These studies were completed as part of an interdisciplinary research team funded by The Moody Project for Translational Traumatic Brain Injury Research.

Keywords: TBI, Tau, Protein aggregation, Tau oligomers, Tau pathology

B2-09

ACUTE REGION OF INTEREST CHANGES IN KEY BRAIN INJURY MARKERS FOLLOWING PENETRATING BALLISTIC-LIKE BRAIN INJURY

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Penetrating brain injury (PBI) is associated with high mortality and morbidity. PBI involves accelerated infiltration of peripheral immune cells and increased edema. However, molecular mechanisms underlying PBI are not widely studied. Here we evaluated changes in key markers of PBI across regions of interest (ROIs) including frontal cortex (FCx), striatum (St), hippocampus (Hc), and residual midbrain (RMb), using the model of penetrating ballistic-like brain injury (PBBI). Injury was induced in anesthetized rats by inserting a probe through the right FCx and St followed by rapid balloon inflation causing a temporary cavity. Key injury markers were evaluated 24h post-PBBI to determine molecular effects in ROIs proximal to the injury tract (FCx, St) versus surrounding areas (Hc, rMb). Targeted proteins were glial fibrillary acidic protein (GFAP), GFAP breakdown products (GFAP-BDPs), spectrin, spectrin breakdown products (SBDPs), B-cell lymphoma-2 (BCL2), BCL2-associated protein X (BAX), amyloid associated protein (APP), APP α- and β- C-terminal fragments (APPαCTF, APPβCTF), and *tau* protein. PBBI ROIs were compared to comparable Sham ROIs (n = 10/group). GFAP levels increased 60% in FCx ($p < 0.05$) and 53% in St ($P < 0.05$). GFAP-BDPs levels increased 262% in FCx ($p < 0.05$) and 1342% in St ($p < 0.01$). Spectrinlevels decreased 75% in FCx ($p < 0.01$) and 53% in St ($p < 0.05$). SBDPs levels increased 251% in FCx ($p < 0.01$), 431% in St ($p < 0.01$) and 156% in RMb ($p < 0.01$). BCL2 levels decreased 63% in FCx ($p < 0.0001$). BAX levels increased 1764% in FCx ($p < 0.0001$), 222% in Hc ($p < 0.05$), 5869% in St ($p < 0.0001$), and 387% in RMb ($p < 0.01$). No significant changes were detected in APP or APPαCTF levels. However, APPβCTF levels increased 330% in FCx ($p < 0.001$) and 1089% in St ($p < 0.001$). Total *tau* levels decreased 30% ($p < 0.01$) in FCx. These results indicate that acute (24 h) alterations in astrogliosis and markers of neurodegeneration are limited to ROIs proximal to the injury tract. However, structural protein abnormalities and pro-apoptotic mechanisms expand into surrounding ROIs. Ongoing studies will evaluate these markers at subacute and chronic time-points post-PBBI.

Keywords: Amyloid, Tau, GFAP, Spectrin, apoptosis

B2-10

BRAIN CATHEPSIN B IS ELEVATED IN BOTH MILD-CLOSED AND SEVERE-PENETRATING TRAUMATIC BRAIN INJURY MODELS

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Comprehensive analysis of key mediators involved in traumatic brain injury (TBI) is tantamount to understanding mechanisms involved in injury progression. Cathepsin B is a cysteine protease implicated in several neurodegeneration and TBI models, such as controlled cortical impact. This preliminary study determined if brain cathepsin B was up-regulated in penetrating ballistic-like brain injury (PBBI) or repeated projectile concussive impact (rPCI). For PBBI and sham/craniotomy controls, coronal brain tissue sections were isolated at various time-points post-injury. Repeated (r)PCI was conducted once daily for 4 consecutive days (d). Control groups received anesthesia alone. Righting-reflex (RR) was determined immediately after injury. Select PCI brain tissue regions were collected 1d after the last concussion. Both pro-($\sim$37–43 kDa) and mature ($\sim$20–25 kDa) Cathepsin B protein levels were determined by western blotting and densitometry (mean +/− SEM arbitrary units (AU)). Enzymatic activity was determined by generation of amino-methyl coumarin (AMC). Comparisons between injured and control groups are discussed (2-tailed, t-Test, $p \leq 0.05$); correlative analysis is indicated (1-way, Pearson *r*). Pro-cathepsin B upregulation in brain slices was monophasic and peaked 2–3 d after PBBI (13.3 +/− 1.2 and 15.2 +/− 2.3 AU) compared to Sham (1.2 +/− 0.1 to 3.1 +/− 1.3 AU). Interestingly, mature cathepsin B was maximally increased 7d after PBBI (384.1 +/− 39.7 AU), versus Sham (174.2 +/− 25.4 AU). In rPCI, pro-cathepsin B was increased to (1.7 +/− 0.5 AU) in the prefrontal cortex (not detectable in sham/anesthesia controls). In this brain region, mature cathepsin B was $\sim$7-fold greater after rPCI (14.2 +/− 3.6 AU) compared to controls (2.2 +/− 1.5 AU); proteolytic activity was marginally increased. Surprisingly, cerebellar proteolytic activity increased nearly 3-fold after rPCI (3.0 +/− 0.6 μmoles) compared to anesthesia alone (1.4 +/− 0.2 μmoles), and positively associated with RR ($r = +0.65$, $p = 0.12$). Conversely, decreased activity in this region was negatively correlated with RR ($r = -0.98$, $p = 0.008$) among anesthesia controls. These findings suggest that brain cathepsin B has a role in multiple TBI models and is linked to neurological deficits.

Keywords: Cathepsin B, Penetrating Ballistic-like Brain Injury, Projectile Concussive Impact

B2-11

MODELING CHRONIC NEURODEGENERATION FOLLOWING NEUROTRAUMA: A MULTIPLE MODEL EXPERIENCE

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Chronic neurodegeneration following neurotrauma is associated with neuropsychiatric and cognitive symptoms. To enhance understanding about the underlying pathophysiology linking neurotrauma to neurodegeneration, a multi-model pre-clinical approach must be established and compared to pre-clinical results of tauopathy patterns seen in post-mortem human samples from athletes. We utilized a scaled and validated rat blast traumatic brain injury model and a controlled, closed-head, acceleration-deceleration mouse model. Tau hyperphosphorylation changes were evaluated by western blot and immunohistochemistry. Elevated plus maze and Morris water maze were employed for behavior. Animals exposed to single blast (50PSI reflected) had increased AT8 in the contralateral hippocampus at 1 month compared to controls ($q = 3.962$, $p < 0.05$). Animals exposed to repeat blast (6 blasts over 2 weeks) had increased AT8 ($q = 8.120$, $p < 0.001$) and AT270 ($q = 4.030$, $p < 0.05$) at 1 month post-injury compared to controls. In the controlled acceleration-deceleration mouse model, no significant difference in AT8 was seen at 7 days, but significant difference was reported at 1 month in the ipsilateral hippocampus compared to control ($q = 4.343$, $p < 0.05$). Tau markers CP-13 ($q = 6.406$, $p < 0.001$) and PHF ($q = 10.58$, $p < 0.001$) were significantly increased in the hippocampi of athletes diagnosed with Chronic Traumatic Encephalopathy. Elevated plus maze data revealed rats exposed to single blast ($q = 3.526$, $p < 0.05$) and repeat blast ($q = 4.206$, $p < 0.05$) spent more time impulsively exploring the open arms compared to controls. Morris water maze testing revealed a significant difference between groups in acquisition times on days 22–27. During the probe trial, single blast ($t = 6.437$, $p < 0.05$) and repeat blast ($t = 8.002$, $p < 0.05$) rats spent less time exploring where the platform had been compared to controls. A multi-model approach with human sample comparison facilitates investigation into important correlates linking neurotrauma to neurodegeneration.

Keywords: Tauopathy, impulsivity, Chronic Traumatic Encephalopathy, Multi-model

B3 Poster Session III - Group B: Axonal Injury

B3-01

DYNAMIC SHEARING DEFORMATIONS IN LIVING HUMAN BRAIN WITH RELEVANCE TO TRAUMATIC BRAIN INJURY

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Diffuse Axonal Injury (DAI) is a devastating type of Traumatic Brain Injury (TBI) due to closed-head trauma. It is a debilitating injury that leads to instantaneous unconsciousness and affects millions of people every year just in the United States. DAI is a primary type of injury, meaning the injury to the axons occurs at the time of the accident as opposed to other secondary factors associated with the injury, which can be delayed in time (e.g. swelling). DAI is a consequence of an injury-causing deformation of an axon, leading to its dysfunction. The exact degree and extent of microscopic injuries are almost impossible to diagnose *in vivo* using existing imaging modalities, including Magnetic Resonance Imaging (MRI).

Scientific computations using the Material Point Method (MPM) were developed to predict dynamic deformations in a person-specific brain subjected to mild rotational accelerations. Data on the anatomy of the human head and fiber substructure in the white matter of the brain was obtained from MRI methods. A simplified form of Holzapfel-Gasser-Ogden model was used as the constitutive model for various tissues in the brain. The material model for white matter of the brain further considered fibrous-substructure and viscoelasticity associated with the tissue. Constants in the constitutive model were calibrated based on literature-reported measurements of mechanical responses. Cerebrospinal fluid was modeled as a non-Newtonian fluid. The results from computations were validated against deformations from *in vivo* experiments using the tagged MRI method. Results suggest: focused shearing strains in the substructures of the brain might occur when the head is violently accelerated or decelerated. The dynamics associated with the shear wave propagation can further amplify the shearing strains in the white matter of the brain. A simulation of an injury-causing rotation of the head will be used to demonstrate the ability of the virtual head model to suggest the likelihood of an injury and the locations of injury.

Keywords: mild rotational accelerations, virtual head model, multiscale model, 3D deformations in person-specific brain

B3-02

A COMPUTATIONAL MODEL OF WHITE MATTER AXON FOR QUANTIFYING ACUTE AND DELAYED INJURY SEQUELAE, WITH APPLICATION TO REPEATED INJURY

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Background: The goal of this work was to quantify the neurophysiological underpinnings of concussion. Diffusion imaging, post mortem studies, and animal models suggest that concussion is associated with the damage to white matter axons. Axon stretching affects sodium channels and myelin insulation at nodes of Ranvier, potentially leading to impaired axonal functionality or axonal degeneration.

Methods: A multi-compartmental approach was adopted to create a model of white matter axons incorporating key features of axonal organization. The model incorporated ion channels, ion transport and diffusion mechanisms, as well as the mechanisms of glial swelling. The geometrical and neurological parameters for different model components were extracted from literature to describe white matter axons in human corpus callosum. The model was programmed in NEURON simulator, which allows studying detailed multi-compartmental models of neural structures.

Results: Axonal injury was simulated as coupled left shift (CLS) of nodal sodium channels properties and/or stretch-induced paranodal demyelination. The generic effect of axonal injury was dose-dependent reduction of axonal signal amplitude and dose-dependent alteration of axonal signal latency. Paranode demyelination caused further reduction of axonal signal amplitude and yielded accumulation of extracellular potassium which facilitated axonal transition to degradation. Glial swelling in response to axonal injury had a protective effect and reduced the axonal sensitivity to repetitive injury occurring on the time-scale of several minutes.

Conclusions: The model results were in a good semi-quantitative agreement with the existing experimental data. This effort is part of a larger goal to link a series of models together in an end-to-end fashion to identify a neurologically based mechanism of concussion. Com-

putational models of axon biomechanics have been developed and are used in conjunction with the present model to complete the linkage of external loading conditions to neurological outcomes. The present model can be used as a platform to study trauma-induced alterations in axonal functionality, mechanisms of axonal resilience to trauma and axon healing and recovery.

Keywords: mTBI, paranode demyelination, potassium, swelling, concussion, repetitive injury

B3-03

THE MICROTUBULE-STABILIZING DRUG EPOTHILONE D INCREASES AXONAL SPROUTING RESPONSE IN AN IN VITRO MODEL OF TRANSECTION INJURY

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The loss and misalignment of microtubules are considered a hallmark feature of the degeneration that occurs after Traumatic Brain Injury (TBI). Therefore, microtubule-stabilizing drugs are attractive as potential therapeutics for use following TBI. Taxol, a widely used anti-cancer drug, has shown promising outcomes in the treatment of various animal models of neural trauma, however, Taxol is not ideal for TBI treatment due to its limited blood-brain barrier (BBB) permeability. Epothilone D (EpoD), another microtubule-stabilizing drug, can penetrate the BBB and hence may be more therapeutically appropriate. We have characterized the effects of EpoD on the post-injury axonal sprouting response of relatively mature cortical neurons in an *in vitro* model of CNS trauma. The number of tau labeled axonal sprouts traversing the injury site was significantly reduced ($p < 0.05$) by 100 nM of EpoD and significantly increased ($p < 0.01$) by 0.1 nM of the drug. Furthermore we found no differences between EpoD and vehicle treated axons with regards to their mean and maximal sprout outgrowth velocity, indicating that EpoD effects the number of axons that sprout but not their net growth. To determine whether this effect was specific to pyramidal neurons, we applied EpoD to cortical neuron cultures derived from Thy1-YFP mice. Low doses of EpoD significantly increased the number of YFP-positive axons that sprouted into the injury site when compared to vehicle treated cultures ($p < 0.05$). Our investigations demonstrate that primary cortical neurons can tolerate relatively high concentrations of EpoD, and importantly that EpoD significantly increases the regenerative response of pyramidal axons in a dose dependent manner. These data suggest that EpoD may be a potent therapeutic for enhancing brain repair following TBI and further studies in our laboratory will aim to characterize the effects of Epo D in an *in vivo* model of trauma using the lateral fluid percussion injury model in adult mice.

Keywords: Microtubule stabilising drugs, Epothilone D, axonal sprouting, Primary neuronal culture

B3-04

DTI CORRELATES OF ATTENTION AND PROCESSING SPEED IN SUB-ACUTE AND CHRONICTRAUMATIC BRAIN INJURY

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Introduction: Diffusion Tensor Imaging (DTI) has allowed investigators to more thoroughly evaluate the effects of traumatic brain injury (TBI). Using DTI, some investigators have been able to establish associations between various brain structures and specific cognitive tasks in chronic TBI (Kraus et al. 2007). We examined the relationship between measures of white matter integrity and performance on standardized neuropsychological tests measuring attention and processing speed in patients who had sustained a TBI at both the subacute and chronic phases.

Methods: Twenty three TBI patients (mean age: 42.1 years) categorized as mild, ($n = 5$) moderate ($n = 15$), and severe ($n = 3$) were evaluated within 90 days and at one year post-injury. At both time points, a 3-Tesla MRI scan was performed, as well as battery of neuropsychological tests. Using the SINAPS software package that includes motion and distortion correction, mean fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were calculated for regions implicated in attention and processing speed.

Results: At the 90 day mark, processing speed correlated positively with FA in the genu of the corpus callosum (CC) ($r = .56$, $p < .007$) whereas RD in the CC body was negatively correlated ($r = -.528$, $p = .01$). Measures of attention were associated with FA in the right inferior fronto-occipital fasciculus ($r = .83$, $p = .003$) and AD in the fornix ($r = .536$, $p = .008$).

At one year post-injury, tests of attention positively correlated with FA in the left anterior thalamic radiation. A greater number of regions were related to processing speed; FA in the left inferior fronto-occiptal fasciculus showed a positive correlation ($r = .550$, $p = .008$). RD and MD in the CC posterior and the fornix were also highly correlated.

Conclusions: These results support the hypothesis that higher FA and lower RD in various axonal bundles are associated with better performance in neuropsychological tests of attention and processing speed.

Keywords: Diffusion Tensor Imaging, Neuropsychology, Attention, Traumatic Brain Injury

B3-05

THERAPEUTIC EFFECTS OF TAMOXIFEN IN SPINAL CORD INJURY

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Tamoxifen (TMX) is a breast cancer medication as it acts as a selective estrogen receptor modulator that can mimic the neuroprotective effects of estrogen, but lacks its systemic side effects. We found that TMX significantly improved the motor recovery of partially paralyzed hind limbs of male adult rats with thoracic spinal cord injury (SCI), thus indicating a translational potential for this cancer medication, given its clinical safety and applicability. To shed light on the mechanisms underlying the beneficial effects of TMX for SCI, we used proteomic analyses, Western blots and histological assays, which showed that TMX treatment spared mature **oligodendrocytes** increased myelin levels and altered reactive **astrocytes**, including the upregulation of the water channels aquaporin 4 (AQP4). AQP4 increases in TMX-treated SCI rats were associated with smaller

fluid-filled cavities whose borders consisted of densely packed AQP4-expressing astrocytes closely resembling the organization of normal *glia limitans externa,* in contrast to large cavities in control SCI rats that lacked *glia-limitans*-like borders and contained reactive glial cells. Given that we found that TMX affects both oligodendrocytes and astrocytes in injured spinal cords, we used an *in vitro* model of glia progenitor cells to test the hypothesis that TMX acts on glia progenitors in injured spinal cords. By using rodent glia progenitors *in vitro*, and different experimental paradigms, we found that TMX induces differentiation of glia progenitors towards both oligodendrocytes and astrocytes. In sum, our data strongly suggest that TMX is a promising candidate for the therapeutic treatment of SCI, in part by promoting differentiation of glia progenitors and by normalizing functions of both oligodendrocytes and astrocytes in injured spinal cords.

Keywords: rat spinal cord injury, motor recovery, tamoxifen, glia progenitors

B3-06

CROSS-SECTIONAL DIFFERENCES IN FRACTIONAL ANISOTROPY WITHOUT LONGITUDINAL EVIDENCE OF RECOVERY BY ONE MONTH POST-CONCUSSION

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Changes in white matter structure are hypothesized as one consequence of sports-related concussion (SRC). However, the timeframe for recovery of these deficits has not been established. We assessed longitudinal changes in fractional anisotropy (FA) in 40 collegiate athletes (20.1 ± 1.4 year old) across acute and sub-acute timeframe post-concussion. Concussed athletes completed serial scanning sessions at one day (T1; $n = 33$, 1.64 days post), one week (T2; $n = 30$, 8.3 days post), and one month (T3; $n = 26$, 32.2 days) post-concussion. Forty-six healthy contact sport athletes served as controls (HC; 20.3 ± 1.5 years old). Structured interviews for anxiety and depression were used to assess concussion symptoms. Diffusion tensor imaging (30 non-collinear directions, b-value = 1000 s/mm^2) was performed using a GE 3-T scanner. Both region-of-interest and voxel-wise analyses were conducted to assess longitudinal and cross-sectional differences in FA. Results demonstrated longitudinal evidence of recovery for both anxiety and depression scores by one month post-concussion ($F's > 20$, $p's < 0.001$). In contrast, no significant differences in FA were observed across the acute and sub-acute period post-concussion. However, cross-sectional comparisons indicated increased FA for concussed athletes at T1 in the bilateral superior longitudinal fasciculi, right sagittal stratum, right forceps minor, right internal capsule, bilateral superior cerebellar peduncles, and left corona radiata. Differences in FA persisted at T2 and T3 relative to HC in all regions ($p's < 0.05$). Exploratory analyses found that return-to-play time was positively correlated with behavioral scores at T1 ($rho's > 0.42$, $p's < 0.05$), and with FA at both T1 and T3 ($rho's > 0.43$, $p's < 0.05$). These results demonstrate that white matter deficits following SRC extend beyond the typical period of symptom resolution for most clinical symptoms (e.g., balance, cognitive testing, and self-reported emotional sequelae). The relationship between FA, clinical measures, and plasma tau concentrations in a subset of participants (19/19/12/18; T1/T2/T3/HC) will be explored in the future.

Keywords: concussion, diffusion, athletes

B3-07

TRANSPLANTATION OF EMBRYONIC SPINAL CORD DERIVED CELLS INTO TRANSECTED PERIPHERAL NERVE TO PREVENT MUSCULAR ATROPHY

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An average human body contains around 45 miles of nerves essential for our life. So what happens when just a small part like one nerve will be injured? In serious injury, the connection between spinal cord and the target organ will be lost resulting in the muscle atrophy. Luckily, regeneration in PNS is possible and many surgical approaches can be implied. However, most nerves in the human body are too long for the slow regeneration and treatment methods to prevent the muscle atrophy during the regeneration time should be applied in addition to the surgical approach. In this project, cells isolated from E14 rat embryos' spinal cords were injected into the distal side of transected musculocutaneous nerve in hope that they are able to prevent the muscle atrophy. We tested cells isolated from spinal cord different segments (cervical, thoracic and lumbar) as well as directly isolated fetal cells that mostly contain neurons (P0 cells) and cultured neural progenitor cells (P2 cells). Our results show that cells were able to survive and help to retain the muscle fiber size that was 31%, 70% and 51% ($p < 0.001$) of uninjured side in control, P0 cell and P2 cell group, respectively. Furthermore, motor endplates in control animals were smaller ($205 \pm 50\ \mu$m) and had either shrunken or fragmented appearance while in cell treatment groups endplates were bigger ($278 \pm 23\ \mu$m in P0 and $241 \pm 11\ \mu$m in P2 cell group) and 20–40% of them showed normal pretzel-like structure. In electromyographic studies, stimulation of transected nerve with cell transplantation was able to induce the response in biceps brachii while no response was seen in the control group. Interestingly, P0 cells survived and were able to reduce muscle atrophy more than P2 cells whereas the cells from lumbar segment showed the best results. In conclusion, cells isolated from embryonic spinal cord are able to reduce the muscle atrophy and therefore they hold a great promise for the future of treatment of peripheral nerve injuries.

Keywords: muscle atrophy, cell transplantation, neuron replacement, fetal spinal cord cells, peripheral nerve injury

B3-08

STABILIZING MICROTUBULES AFTER TRAUMATIC AXONAL INJURY MITIGATES ACCUMULATION OF TAU, CALCIUM INFLUX AND AXONAL DEGENERATION

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Introduction: Traumatic axonal injury (TAI), a common consequence of traumatic brain injury (TBI), can result in mechanical damage of microtubules and influx of calcium, in concert with unbinding of the microtubule-stabilizing protein, tau, in axons and its accumulation in the neuronal soma. Here, we examined the effects microtubule stabilization treatment using Taxol on outcome of TAI using a well-characterized in-vitro model of dynamic axon stretch-injury.

Methods: Primary cortical neurons were grown on micropatterned deformable silastic membranes, whereby a series of parallel 2 mm-long lanes containing only axons spanned two populations of neuronal

soma. The axon region was rapidly stretched via mechanical parameters based on clinical TBI. Taxol was applied either 30 mins before injury, 5 or 15 mins post-injury. Immunocytochemical analysis was performed at 1, 24, 48 hrs post-injury for Ankyrin-G, total-tau and phospho-tau AT8, AT270 and S404. In addition, calcium influx using the calcium indicator Fluo-4 and the number of surviving axons was assessed.

Results: Microtubule stabilization with Taxol prior to TAI resulted in: 1) apparent maintenance of the axon initial segment (AIS) diffusion barrier, 2) decrease in somal total-tau and phospho-tau accumulation, beginning within 1 hr post injury and continuing though 48 hrs, 3) a substantial mitigation of intra-axonal increases in calcium concentration. While post-injury treatment did not dramatically influence these outcomes, like pre-treatment, it did decrease in the number of degenerating axons observed at 24 hrs.

Conclusions: These in-vitro data demonstrate that enhancing axonal microtubule stability can substantially improve outcome and axon survival after TAI. Taxol protection of the AIS barrier may account for reduced accumulation of tau in the cell-soma. In addition, Taxol treatment mitigates progressive calcium influx into axons after injury, potentially by maintaining cytoskeletal structure and reducing ion-channel dysregulation. Moreover, the observation that microtubule stabilization after injury promotes axon survival, suggests that taxane treatment may have potential therapeutic value for clinical TBI.

Acknowledgments

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Keywords: traumatic axonal injury, phosphorylated tau, calcium

B3-09

FUNCTIONAL ALTERATIONS IN INTRINSIC AND SYNAPTIC PROPERTIES 1 MONTH AFTER MILD TRAUMATIC BRAIN INJURY

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Mild traumatic brain injury (mTBI) produces long lasting cognitive dysfunction without cell death but with diffuse axonal injury. Using YFPh mice allows identification of the axonal condition of layer V pyramidal neurons in somatosensory cortex after central fluid percussion injury. Using this paradigm with 1–2 day survival period, we have previously shown alterations in both intrinsic and synaptic properties of intact (IT) and axotomized (AX) neurons. Here we examined these properties at 32–40 days. Excitatory post synaptic currents (EPSCs) and inhibitory synaptic currents (IPSCs) were recorded in voltage-clamp mode at −50 mV and +10 mV respectively QX-314 in the patch solution). Measures are reported as mean ± SEM, and compared with t-tests, with $n \geq 9$ cells and significance at $p < 0.05$.

The action potential amplitude was increased in both AX and IT neurons at 32–40 days. The percentage of intrinsically bursting (IB) neurons was previously shown to be decreased at 2 days in the IT population, with this longer survival period the percentage of IB neurons showed a trend toward being increased in the IT (50%, z-test, $p = 0.054$) compared to sham (17%) with AX neurons at 36%.

The frequency of spontaneous (s) EPSCs was significantly decreased in the IT population compared to both control and TBI AX neurons. Neither area nor amplitude of sEPSCs were altered. The miniature (1 mM TTX in bath) EPSCs showed the same trend, suggesting that there may be a compensatory reduction in the number of excitatory synapses on intact neurons. There was no change in the frequency, amplitude or area of sIPSCs in either AX or IT compared to controls. However, the frequency of mIPSCs was significantly decreased in IT neurons compared to controls. The ratio of the frequency of excitatory to inhibitory events (E/I_R) for spontaneous events was significantly lower in IT neurons compared to control cells. The E/I_R for miniature events was not different from control.

These data suggest that some recovery occurs in the network after the initial hyperexcitability and that compensatory activity-lowering mechanisms take place in IT neurons.

Supported by NIH-NS077675.

Keywords: EPSCs, IPSCs, Intrinsic properties, action potential

B3-10

ALTERED GABAERGIC SYNAPTIC TRANSMISSION IN LAYER V PYRAMIDAL NEURONS AFTER MILD TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) is a major cause of disability and sometimes produces epilepsy. We recently demonstrated epileptiform fields after a mild injury in mouse in which layer V pyramidal neurons had an increased frequency of miniature-excitatory-postsynaptic-currents. Since network excitability is also affected by inhibition, here we examined overall inhibition and that due to optogenetically selective activation of somatostatin-containing GABAergic interneurons(SS). Mice selectively expressing channelrhodopsin in SS were given a mild, central fluid percussion or sham injury. Whole cell patch clamp was used to record spontaneous, electrically evoked and light-evoked inhibitory postsynaptic currents (s-, e-, l- IPSCs) in layer V pyramidal neurons, 1–2 days after injury with glutamate receptor antagonists in the bathing medium. The s-IPSC frequency was significantly increased (9.7 ± 1.0 for 6 TBI and 6.0 ± 1.6 Hz for 6 control neurons, t-test, $p < 0.05$), while amplitude was unchanged. The e- and l-IPSCs were recorded across a series of 5 intensities, induced with increasing duration of stimulation located $\sim 100\,\mu$m lateral to the recorded neuron. For evoked IPSC comparisons, repeated measures ANOVAs were employed. The peak e-IPSC was not significantly different between control and TBI ($n = 11$ control and 9 TBI). Light was applied to activate channelrhodopsin through the 60X objective, positioned over the electrical-stimulating electrode. The l-IPSC was significantly greater in TBI compared to controls ($n = 16$ control and 9 TBI, $p < 0.05$). In some of the same neurons, light and electrical stimulation were applied simultaneously. While in controls the addition of the light did not significantly change the peak IPSC, in TBI neurons light significantly suppressed the IPSC. Direct comparison between control and TBI neurons for the condition of electrical + light stimulation showed a significantly reduced IPSC peak in TBI neurons ($n = 5$ neurons each in control and TBI, $p < 0.05$). Together these results suggest that SS interneuron output is enhanced after TBI, but that the network consequence of this may be to produce disinhibition through the suppression of output from other inhibitory cell types. Supported by NIH grant NS077675.

Keywords: Optogenetics, channelrhodopsin, somatostatin interneurons, cortical interneurons, IPSCs

B3-11

ADVANCED DIFFUSION MRI METHODS TO QUANTITATIVELY DISTINGUISH BETWEEN COMPLEX WHITE MATTER AND TRAUMATIC AXONAL INJURY

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Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative condition that occurs following repetitive mild traumatic brain injury. Its distinct neuropathological features, including phosphorylated tau tangles and axonal degeneration, can be detected postmortem via staining, but remain invisible to current imaging methods. Diffusion weighted imaging has been proposed as a noninvasive detection method due to its high sensitivity to microstructural changes in brain tissue integrity. This approach is complicated by the assumption that diffusion in a voxel can be modeled using a single Gaussian distribution, leading to ambiguous results when attempting to distinguish axon degeneration from uninjured regions with complex fiber architecture. We demonstrate through alternative diffusion imaging methods and quantitative histology that diffusion imaging can distinguish between complex fiber architectures and injured axon regions.

Human ex vivo cortical tissue was scanned using an 11.7T Varian MRI scanner, 202 diffusion weighted gradient directions, and a voxel size of 250x250x500 μm. Diffusion based directionality was calculated using both diffusion tensor and generalized q-space (GQI) models. The tissue was then serially sectioned into 50 μm slices and stained for myelinated axons using Black Gold II. Two dimensional Fourier transforms of Black Gold II stained images were used to quantify histological fiber directionality of each 250x250x500 μm region. Registration of the histological data to the diffusion data was performed by placing landmarks in both data sets and applying a similarity transform to the histological image.

Using an ROI based analysis, we found that regions with complex distributions of fiber orientations also had reduced fractional anisotropy in diffusion tensor imaging, while the generalized fractional anisotropy from GQI was not reduced. These findings demonstrate that advanced diffusion weighted imaging can account for complex white matter structures and is likely provide a more specific means of quantitatively assessing axon directionality and injury.

Keywords: Ex vivo study, Diffusion weighted imaging, Fiber direction, Histological correlation

B3-12

BLAST INDUCED SPATIAL AND TEMPORAL ALTERATIONS IN GLIAL EXPRESSION AND AXONAL INJURY IN THE RAT SPINAL CORD

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Blast induced neurotrauma is a signature wound of veterans returning from military operations. With much of the research focus being directed at understanding blast wave induced changes in the brain knowledge related to blast effect in the spinal cord remains unresolved. Knowledge related to injury changes in the spinal cord following blast overpressure may help understand altered sensory problems often reported by veterans. In fact, a high prevalence of chronic pain, particularly in the back (58%) and head (55%) in some veterans was also reported. Whether blast overpressure induces injury changes in the spinal cord and if these changes contribute to acute or chronic sensory changes is a fundamental question that is yet to be addressed. We postulate that blast overpressure induces changes in the spinal cord in the form of glial activation and axonal injury. Anesthetized male SD rats were subjected to a single insult of blast overpressure (22 psi) induced by a custom-built shock tube. Rats were divided into groups based on their survival period: 6 hours, 24 hours, 3 days and 7 days. The spinal cord segments (cervical, thoracic and lumbar) were cut horizontally into 40 μm thick serial sections. Astrocytic and microglial activation was revealed by Glial fibrillary acidic protein (GFAP) and ionized calcium-binding adapter molecule 1 (Iba1) immunohistochemistry. Axonal injury was revealed by neurofilament light chain immunohistochemistry. The extent of astrocytic and microglial activation was quantified by counting their number from representative images taken from cervical, thoracic and lumbar spinal cord sections. Elevated astrocyte and microglial counts were observed in blast spinal cord compared to sham. Temporally, significantly high astrocytes were observed in different regions of the spinal cord. Axonal injury changes were observed in all spinal cord segments at various time periods after blast. Taken together these findings support that blast induced injury changes extend into spinal cord and may contribute to altered neuronal function.

Keywords: Shock tube, Blast induced spinal cord injury, Rats, Astrocytic and microglial activation

B3-13

OPEN FIELD PRIMARY BLAST EXPOSURE INDUCES NEURONAL AND GLIAL ALTERATIONS IN FRONTAL CORTEX

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The wars in Iraq and Afghanistan have highlighted the emergence of Blast Induced Neurotrauma (BINT) and the associated mild traumatic brain injury as the signature wound in returning service members. Several animal studies showed axonal injuries, myelin and cytoskeletal breakdown, cell death and glial activation as part of efforts in understanding the pathological changes in brain after blast. However, detailed studies aimed at characterizing cellular injury changes in a gyrencephalic primary blast exposure model are still limited which forms the purpose of this study. Anesthetized male Yucatan swine (50–60 kg) were exposed either to medium (224–332 kPa; n = 7) or high overpressure (350–403 kPa; n = 5) open-field blast. Sham animals (n = 5) were not subjected to blast. After a 3-day survival period, the frontal cortex of the perfused brain was cut into 5 mm blocks which were then cut into 40 μm thick serial sections. Sections were then processed to assess axonal injury (β-APP-beta amyloid precursor protein), glial proliferation (glial fibrillary acidic protein; ionized calcium-binding adapter molecule 1) and cellular injury (cleaved caspase 3 and H&E staining). Prominent diffuse axonal injury in the form of β-APP immunoreactive swollen axons and retraction balls was observed in the high overpressure group. Also observed were prominent white and grey matter β-APP reactive zones in the high-overpressure brain sections compared to medium overpressure and sham brain sections. β-APP reactive zones were reminiscent of Amyloid β staining in Alzheimer's. Also observed was elevated astrocyte counts in both the blast groups. A significant number of microglia were also observed in medium pressure compared to sham. Our findings support the presence of prominent axonal injury and β-APP reactive immunoreactive zones in these frontal cortical regions following primary blast exposure. Prominent astrocytic and microglial proliferation also suggests potential inflammatory changes. These findings suggest a putative role for an altered neuroglial homeostasis in the etiology of primary blast induced neurotrauma.

Keywords: Swine, Primary blast induced brain injury, Open field blast, β-APP-beta amyloid precursor protein, Astrocytic and microglial proliferation,

B3-14

BIOMECHANICAL RESPONSE, NEUROPATHOLOGY AND BIOMARKER EXPRESSION IN AN EXPERIMENTAL MODEL OF TRAUMATIC BRAIN INJURY

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There is a lack of traumatic brain injury models that correlate measured biomechanical response, neuropathology and levels of biomarkers that reflect the severity of brain injury. This study uses a head impact model which correlates quantified biomechanics to axonal histology, and serum and CSF biomarker expression in determining TBI severity. Anesthetized male Sprague-Dawley rats were subjected to TBI using a head impact device from 1.25, 1.75 and 2.25 m drop heights. Linear and angular head kinematics were measured with miniature transducers. Twenty-four hours post-trauma, CSF and blood were collected and levels of amyloid beta (Aβ)1-42, neurofilament H (NF-H), glial fibrillary acid protein (GFAP) and interleukin (IL-6) were assessed by ELISA. Traumatic axonal injury (TAI) was quantified as the total number of β-APP-reactive axonal swellings/retraction balls in the corpus callosum (CC) and pyramidal tract (Py). Compared to controls, significantly higher CSF and serum NF-H levels were observed, except in 1.25 m-group in serum. CSF and serum NF-H levels at 2.25 m were significantly higher than at other heights, and CSF and serum NF-H levels at 1.75 m were significantly higher than at 1.25 m. In both CSF and serum, GFAP levels were significantly higher at 2.25 m than other groups/controls. GFAP levels at 1.75 m and 1.25 m were significantly higher than in controls. TBI rats also showed significantly higher levels of IL-6 versus control. Aβ levels were not different among impact groups/controls. CSF GFAP was the best single biomarker (AUC = 0.946) followed by CSF NF-H (AUC = 0.938). Serum GFAP (AUC = 0.920) and NF-H (AUC = 0.85) had better predictive abilities than the others. Correlations between biomechanical parameters, biomarker levels, and TAI numbers indicated that NF-H and GFAP in CSF and serum were reliable predictors for severe TBI in this model, whereas CSF NF-H and CSF and serum GFAP were good indicators for mild TBI. Both CSF and serum NF-H correlated well with quantified TAI in CC and Py, suggesting they are directly related to the severity of the mechanical trauma to the brain.

Keywords: rodent impact head injury, biomechanical measurements, axonal pathology, serum and CSF biomarker

B3-15 (See D8-01)

NECK STRENGTH IS ASSOCIATED WITH HISTORY OF CONCUSSION IN AMATEUR ADULT SOCCER PLAYERS

Eva Catenaccio

B4 Poster Session III - Group B: Epilepsy/Seizure

B4-01

PROGRESSIVE SEIZURES FOLLOWING MICROGLIAL ACTIVATION AND INFLUX OF PROFESSIONAL APCS IN AUTOIMMUNE TARGETING OF ASTROCYTES

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Brain injury-related inflammation results in increased susceptibility to seizures and epilepsy, as well as migraine. Innate immune signaling, including proinflammatory cytokine modulation of astrocytic function, has been implicated in epileptogenesis. Far less is known about the role of adaptive immunity, although T cells have been found in brain tissue of both epilepsy patients and experimental animals following seizure. To determine whether an antigen-driven response against a non-neuronal target can be sufficient to initiate epilepsy, we generated mice with CD4 T cells targeted against an astrocyte-expressed molecule. Following adjuvant stimulation, animals developed visually overt seizures. We looked at the progression of events leading up to seizures to find: 1) progressive infiltration of macrophages and B cells; 2) infiltration of IFNγ-producing T cells throughout brain; 3) progressive activation of microglia; 4) astrogliosis. Unlike brain-infiltrating antigen presenting cells (APCs), microglia expressed low levels of molecules regulating T cell activation, phagocytosis, and inflammatory responses, but upregulated many of these molecules over the course of disease progression. This suggests that microglia may be more plastic and are able to progressively become highly activated, providing a greater contribution to inflammatory signaling and regulation of T cell responses later into epileptogenesis. However, APCs appear to have a greater capacity to phagocytose and produce inflammatory responses, and thus are likely the determinants of disease initiation. Here we show that autoimmune targeting of astrocytes, and not neurons, can result in progressive seizures. Using this model, we can manipulate the contribution of distinct immune cell types to progression of epileptogenesis. For example, to determine whether eliminating T cells or B cells after seizures develop can 1) halt or reverse disease progression, 2) not affect seizure progression once adaptive immunity-mediated initiating events have occurred, or 3) alternatively, whether T cells become protective in later stages of disease.

Keywords: microglia, T cell, macrophage, adaptive immunity

B4-02

NEURONAL GLUTAMATE TRANSPORTER GENETIC VARIATION: IMPACT ON EPILEPTOGENESIS AND EPILEPSY RISK FOLLOWING SEVERE TBI

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Post-traumatic seizure (PTS) is a well-recognized complication following severe traumatic brain injury (sTBI). Risk factors for PTS have been identified, but there remains variability in predicting who will develop PTS. Secondary injury cascades like excitotoxicity may influence epileptogenesis following sTBI. Glutamate transporters manage glutamate levels and excitatory neurotransmission physiologically and can be disrupted in both epilepsy and TBI. We hypothesized genetic variation in neuronal glutamate transporter genes would be significantly associated with epileptogenesis and increased PTS risk

after sTBI. Subjects 18–75 yrs with sTBI were assessed for genetic relationships with PTS. Genetic variants within neuronal glutamate transporters, SCL1A1 and SCL1A6, were screened for 253 individuals. Kaplan-Meier curves, compared with log-rank statistics, were used to estimate seizure rates from admission to 3 yrs and 2 days post-injury through 3 yrs post-injury for SNPs by genotype. Cox proportional hazards regression was used to estimate hazard ratios for SNPs significant in Kaplan-Meier, adjusting for known risk factors. 32 SNPs were examined (SLC1A1: n = 28, SLC1A6: n = 4). 49 (19.37%) subjects had PTS. Of these, 18 (36.73%) subjects seized within 7 days, and 31 (63.27%) seized 8 days-3 yrs post-TBI. Correcting for multiple comparisons, rs10974620 (SLC1A1) was significantly associated with time to first seizure across the 3 yr follow-up (seizure rates: 77.1% minor allele homozygous, 24.8% heterozygous, 16.6% major allele homozygous; $p = 0.001$). When beginning PTS follow-up on day 2, rs7858819 (SLC1A1) was significantly associated with PTS risk (seizure rates: 52.7% minor allele homozygous, 11.8% heterozygous, 21.1% major allele homozygous; $p = 0.002$). After adjusting for covariates, rs10974620 but not rs7858819, remained significant (rs10974620: $p = 0.018$; HR: 5.24, 95%CI: 1.67–16.48, minor allele versus major allele homozygous). Genetic variation within SCL1A1, specifically rs1094620 and rs7858819, is associated with epileptogenesis following sTBI, as demonstrated by time-to-event analyses. Future studies are needed to confirm findings, but variation within neuronal glutamate transporter genes may represent a possible therapeutic target for pharmacological PTS prevention.

Keywords: rehabilomics, epileptogenesis, genetic variation, neuronal transmitters, glutamate, TBI

B4-03

COMPARISON OF FACTORS PREDICTING POST-TRAUMATIC SEIZURE AT 1, 2, & 5 YEARS POST-INJURY: A TBIMS ANALYSIS

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Post-traumatic seizures (PTS) occur frequently following traumatic brain injury (TBI). Published PTS prevalence rates depend on study characteristics, and there is limited information regarding long-term differences in PTS risk factors over recovery. Therefore, we developed logistic regression models, describing the most important factors related to PTS at 1, 2, & 5 years post-TBI. Data were collected from the TBI Model Systems National Database, a multi-center longitudinal study examining long-term recovery and outcomes after TBI. PTS prevalence at each time-point was calculated. Baseline history and injury characteristics were selected *a priori* from risk factors identified in previous studies and biological plausibility. Subjects with missing data were excluded at individual time-points. For each model: Univariate logistic regression for each variable of interest was performed; effect size and significance were calculated. Variables were ranked by level of significance, and those with $p > 0.20$ excluded. A main effects model was then fit. Forward and backward regression were then performed, and variables excluded if $p > 0.10$ in forward, and if $p > 0.05$ in backward regression. All models controlled for injury year. Fit was assessed using Hosmer-Lemeshow Goodness-of-Fit Test. At years 1, 2, & 5: 4,236, 2,991, and 1,176 subjects had complete data. At each follow-up, acute hospitalization seizure (all $p < 0.0001$; OR: 3.37, 3.28, 5.13) and craniectomy (all $p < 0.0001$; OR: 2.86; 2.19; 2.51) were the most significant predictors. All models include craniotomy, penetrating TBI, and subdural hematoma. Additional significant variables include: (year-1) post-traumatic amnesia duration and pre-injury incarceration, (year-2) contusion load, race, and pre-injury cognitive limitation, (year-5) contusion load and race. Some PTS risk variables are dynamic, while the most significant remain consistent across the follow-up period. Some variables (e.g. incarceration) may be proxies for latent risk factors; others (e.g. acute-care seizure, craniectomy) could inform risk associated with clinical practice, justify prophylactic therapies development research, and support experimental PTS model development.

Keywords: Rehabilomics, TBI, population risk factors, prediction modeling, PTS

B4-04

EFFECTS OF LEVETIRACETAM AND GABAPENTIN COMBINATION THERAPY ON POST-TRAUMATIC NON-CONVULSIVE SEIZURES (NCS) INDUCED BY A PENETRATIN

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When tested as monotherapies, levetiracetam (LEV) and gabapentin (GBP) showed different anti-seizure dose-response profiles against nonconvulsive seizures (NCS) induced by penetrating ballistic-like brain injury (PBBI) in rats. LEV (12.5–100 mg/kg) reduced NCS frequency and duration in a dose-dependent fashion whereas the anti-seizure effects of GBP appeared to plateau across the dose-range tested (12.5–25 mg/kg). The current study tested a series of fixed-dose ratios of the LEV + GBP combination to determine if combining these two drugs would produce additive or synergistic effects. All rats received frontal PBBI, immediately followed by continuous EEG monitoring for 72 h. LEV + GBP treatment (LEV/GBP: 6.3/0.62, 12.6/1.25, 25/2.5, 50.7/5.0, 101.4/10.0 mg/kg) was administered intravenously twice/day for three days, initiated 30 min post-injury. Control animals received matching vehicle treatments. Compared to vehicle-treated group, LEV + GPB combination therapy reduced PBBI-induced NCS incidence from 69% (vehicle group) to 27–65% and delayed NCS onset latency from 12.3h (vehicle group) to 19.1–57.8h across all LEV + GBP treated groups. Among the five dose ratios tested, the most significant anti-seizure effects were afforded by the three highest dose ratios (25/2.5, 50.7/5.0, and 101.4/10.0 mg/kg) as evidenced by the dose-dependent reduction in NCS frequency (34%, 45%, and 64%), and shortened NCS duration (44%, 59% and 58%), respectively ($p < 0.05$ vs. vehicle treatment for each measure). However, the dose equivalence analysis indicated that the observed anti-seizure effects of the LEV + GBP combination failed to achieve additivity or synergism. Consequently, these findings showed that a LEV + GBP combination therapy replicated the dose-response profile of LEV monotherapy, but did not benefit from the addition of GBP to improve their anti-seizure activities. Hence, any advantage in simultaneous usage of these two drugs appears limited.

This research was funded by the Army Combat Casualty Care Research Program.

Keywords: Combination Therapy, Penetrating brain Injury, Levetiracetam, Gabapentin, Isobolographic analysis

B4-05

SYNERGISTIC EFFECTS OF PHENYTOIN AND ETHOSUXIMIDE AGAINST POST-TRAUMATIC NONCONVULSIVE SEIZURES

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A key aspect of isobolic analysis of combination therapy is to determine the proper dose ratios of two drug constituents to achieve expected synergistic effects. Recently we demonstrated that combined treatment of phenytoin and ethosuximide (PHT + EXM) at a fixed dose ratio (PHT/EXM: 14.4/44.4 mg/kg) achieved *additive* effects on attenuating nonconvulsive seizures (NCS) induced by penetrating ballistic-like brain injury (PBBI) in rats, but not *synergism* as defined by the isobolic analysis method. In this study we tested a set of variable dose ratios of PHT + 2EXM combination, such that one part of PHT was paired with two parts of EXM in reference to the fixed dose ratios tested previously, i.e. 0.9/5.5, 1.8/11.1, 3.6/22.2, 7.2/44.4, or 14.4/88.98 mg/kg (PHT/2EXM). All rats received frontal PBBI followed by 72-h continuous EEG monitoring. The treatments were delivered intravenously twice/day for three days (first injection initiated 30 min post-injury). Control animals received matching vehicle treatments. The results showed that PHT + 2EXM reduced NCS incidence from 75% (vehicle group) to 44–56% ($p > 0.05$) and significantly delayed NCS onset latency from 22h (vehicle group) to 41–52h post-injury ($p < 0.05$) across all PHT + 2EXM groups. PHT + 2EXM treatments also decreased NCS frequency by 29–76% and shortened NCS cumulative duration by 3–77% compared to vehicle treatments. For these latter two measurements, the most significant effects were afforded by the three low dose ratios of PHT + 2EXM combination ($p < 0.05$). More importantly, the dose equivalent analysis indicated that the observed efficacy of these three dose ratios *achieved synergism* when compared to the expected efficacy. The results of this study not only demonstrated that enhanced anti-seizure efficacy was provided by the reduced dosages of PHT and EXM as a combination therapy, but also emphasize the importance of testing proper dose ratios of any two drugs in achieving objectively defined synergism.

This research was funded by the Army Combat Casualty Care Research Program.

Keywords: Combination Therapy, Penetrating Brain Injury, Phenytoin, Ethoxusimide, Isobolographic Analysis

B5 Poster Session IV - Group B: Function

B5-01

SUICIDAL IDEATION IN THE FIRST 6 MONTHS POST-MILD TRAUMATIC BRAIN INJURY

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Purpose: The aims of this study were to 1) assess the prevalence of suicidal ideation (SI) in persons post-mild traumatic brain injury (TBI) compared to control non-injured subjects and 2) to examine if demographic or social factors increase risk of SI endorsement to 6 months post-mild TBI.

Protocol/Methods: This was secondary data analysis of an ongoing cohort study. Cohorts under study include those with mild TBI (via CDC definition) and non-injured age/gender matched controls. Demographic characteristics and social support (MOS Social Support Scale-MOS-SSS) were assessed at baseline. Suicidal ideation was endorsed if subjects scored 1 or higher on question 17 of the Brief Symptom Inventory-18 (BSI-18). The BSI-18 was administered at day 7, 1, 3 and 6 months post-injury/enrollment. Chi-squared and logistic regression analyses were used, with a significance level set a $p < 0.05$.

Results: Data were available on 256 subjects ($n = 135$ mild TBI; $n = 121$ non-injured controls). The prevalence of persons endorsing any SI was higher in those with mild TBI (16.3%) compared to non-injured controls (11.6%), but this difference was not statistically significant ($p = .18$). Similar differences were seen between those expressing being bothered moderately or more by thoughts of ending their life in the past 7 days (7.4% TBI vs. 4.9% of control). The prevalence of SI was slightly lower in persons 55 and older following TBI (15%) compared to younger individuals (17.3%). Of the demographic and social variables only social support was a significant predictor of SI. For every one point increase in the MOS-SSS, the risk of endorsing SI decreased by 4% (95% CI 1.5–7%).

Conclusion: While there is prevalent SI in community-dwelling persons following mild TBI, the rate was no higher than that of a matched cohort of non-injured persons. Interventions that increase levels of social support are needed to improve mental health post-injury.

Supported by NIH/NINDS R01NS077913

Keywords: mental health, aging, social support

B5-02

MONITORING SENSORY FUNCTION AFTER CERVICAL SPINAL CORD INJURY IN NON-HUMAN PRIMATES

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A recent query of a large multicenter, multispecies spinal cord injury (SCI) database (i.e., VISION–SCI) revealed that sensory outcomes are rarely assessed in preclinical SCI models (10.2%) compared to motor outcomes (59.1%). Sensory measures are important to further translational research to screen for (mal-)adaptive changes in sensation. Efforts linking outcomes across species are crucial to relate knowledge of mechanism gained in preclinical research to clinical symptoms. Towards this goal von Frey hair (VFH) assessments were performed in a non-human primate cervical (C6-C7) hemi-contusion model of SCI. Four animals were assessed during early, mid- and late recovery periods at 5 sites (i.e., shoulder, hand, thorax, knee and foot). The response to the electronic VFH stimulus was classified into 4 categories: no response, segmental responses (withdrawal, skin contraction or flinch), supraspinal responses (orientation, activity arrest) and facial supraspinal responses (wince and vocalization). Data were

analyzed using a generalized estimating equation. Statistical analysis of the response categories revealed that time affected the VFH response (Wald Chi-Square = 11.146, p = 0.004). Further the 5 body locations assessed behaved differently over time (time*location effect; Wald Chi-Square = $2.197*10^{13}$, p < 0.0001). Post-hoc analysis indicated that the animals were particularly responsive to stimulations at the thorax at the intermediate time-point (Chi-Square = 9.750, p = 0.008). Overall, these data suggest differences across sites in responsivity, and that changes in responses were distinct at the thorax in the intermediate post-op period. The VFH testing provided a means of evaluating potential changes in sensation as reflected by tactile sensitivity. The long term goal of these efforts is to pave the way for improved cross-species sensory testing, and accelerate translational research.

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Keywords: Spinal cord injury, Sensory system, von Frey hair, translational research

B5-03

OUTPATIENT CARE REFERRAL AT 3-MONTHS IS ASSOCIATED WITH 6-MONTH SYMPTOMATOLOGY FOLLOWING MILD TRAUMATIC BRAIN INJURY

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Current guidelines for mild traumatic brain injury (mTBI) are not clearly defined, and the relationship between referral of care and chronic symptoms after mTBI needs better characterization. We utilized the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) Pilot study to investigate whether referral of care influences 6-month functional outcome on the Glasgow Outcome Scale-Extended (GOSE) and post-concussive syndrome (PCS) domains on the Acute Concussion Evaluation (ACE). Of 168 mTBI patients (age 45 ± 18 years, 69% male), 22% received referral by 3-months post-injury. Education years (OR 0.85, 95% CI [0.76–0.96], $p = 0.011$), psychiatric history (2.73, [1.30–5.75], $p = 0.008$) and GCS < 15 (2.71, [1.17–6.25], $p = 0.020$) emerged as predictors of 6-month functional disability after adjusting for age, CT pathology and 3-month referral. Referral was not a predictor of GOSE. Regarding PCS, patients with 3-month referral reported a higher incidence of 6-month cognitive and physical symptoms (78%/58%, $p = 0.024$; 89%/70%, $p = 0.020$, respectively). On multivariable regression, 3-month referral (OR 3.15, [1.25–7.92], $p = 0.015$), less education years and psychiatric history predicted the presence of 6-month cognitive symptoms, while referral (OR 3.31, [1.05–10.38], $p = 0.040$) and psychiatric history predicted physical symptoms. Education, psychiatric history, GCS < 15 and CT were adjusted predictors of sleep symptoms, and only psychiatric history predicted emotional symptoms. Hence, patients seeking subacute referral post-mTBI may indicate a population at risk for residual cognitive and physical PCS symptomatology. More granular information regarding the incidence of outpatient services should be collected to better triage and allocate resources to this population.

Keywords: Clinical Trial, Human Studies, Mild TBI, Outcomes, Outpatient Care

B6 Poster Session IV - Group B: Imaging

B6-01

IS DTI A NEUROIMAGING MARKER FOR MTBI WITH LOSS OF CONSCIOUSNESS?

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Objectives: To study whether loss of consciousness (LOC) in mTBI is associated with injury to white matter (WM) tracts in patients with normal CT scans.

Methods: Seventy-nine patients with mTBI and 64 orthopedic injury (OI) controls had diffusion tensor imaging (DTI) at the initial study visit (mTBI mean = 25.9 hrs post-injury, SD = 12.3 hrs; OI mean = 29.8 hrs, SD13.7) and 3 months (mTBI mean = 94.4 days, SD = 8.7; OI mean = 96.7 days, SD = 9.0) post-injury. LOC was determined from EMS records, witnesses, and self-report. DTI was performed on a 3T Philips scanner using a 32 direction protocol. Fractional anisotropy (FA) and mean diffusivity (MD) were measured using tractography for the uncinate fasciculi (UF) and inferior frontal occipital fasciculi (IFOF).

Results: Forty-nine (62.03%) mTBI patients had LOC (mean = 3.84 min, SD = 4.8), whereas 30 (37.97%) did not. On the initial DTI, mTBI patients with LOC had significantly higher MD (right UF = .773, left UF = .782, right IFOF = .764, left IFOF = .783) than OI patients (right UF = .761, left UF = .770, right IFOF = .755, left IFOF = .772), p < 0.05 for all four tracts, effect sizes, Cohen's d were 0.54, 0.48, 0.44, and 0.45, respectively). However, MD in the mTBI subgroup without LOC (right UF = .761, left UF = .778, right IFOF = .762, left IFOF = .779) did not differ from the OI group and effect sizes were 0.22, 0.08, 0.13, and 0.30 respectively). LOC in mTBI group had a positive relation to MD in right UF (slope = 0.002, p < 0.0001) and left UF (slope = 0.0016, p = 0.0034) and the slope did not significantly change between initial and 3 month occasions. LOC duration was also significantly related to MD in right IFOF (slope = 0.0012, p = 0.0243) and left IFOF (slope = 0.0011, p = 0.0118). LOC had no significant relation to FA.

Conclusion: LOC in mTBI patients with normal CT is related to diffusivity measured ≈ 24 hours post-injury in WM tracts connecting prefrontal with temporal and posterior cortical regions. Diffusivity at ≈ 24 hours post- mTBI with LOC is greater than in OI patients, whereas MD after mTBI without LOC does not differ from OI. High MD may be useful as a biomarker for mTBI with brief LOC and normal CT.

Keywords: mTBI, DTI, Consciousness, Subacute

B6-02

STREAMLINING PARTICIPANT RECRUITMENT FOR TBI AND PTSD RESEARCH STUDIES

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Objectives: Recruitment of participants for TBI and PTSD studies is a major challenge, which can cause delays in study timelines and even study failures. To address this challenge, the CNRM Recruitment Core works on two screening studies that recruit civilian and military subjects for TBI and PTSD studies. The Core developed procedures and tracking tools for initial identification, screening, and referral of participants from these screening studies to a broad cross-section of CNRM studies.

Methods: Referral of participants to other CNRM studies involves three critical steps: 1) assessing eligibility; 2) gauging participant interest; and 3) making referrals. Tracking tools were developed and implemented to track the eligibility of participants for various studies and the flow of participants from one study to another. To minimize participant burden and to maintain data integrity, participants are referred to only one study at a time, with referral to subsequent eligible studies only after enrollment outcome for the first referred study has been determined. A centralized online database was utilized to streamline the eligibility and referral process.

Results: As of Apr 4, 2015, 598 (88%) of the enrolled participants from the two screening studies have been assessed for eligibility for active CNRM studies, of which 183 participants have been referred to at least 1 study; 62 to 2 studies; and 21 to 3 or more studies. Referrals have led to 73 total enrollments into CNRM studies: 59 participants in 1 study; 4 in 2 studies, and 2 in 3 studies. Common reasons for exclusion from studies include age, date of injury, severity of injury, contraindication to MRI, state of residence, and military status.

Conclusion: Streamlining the referral process will help studies meet their timeline and target. It will also allow studies to focus primarily on science instead of investing efforts on participant recruitment.

Keywords: Recruitment, TBI, PTSD, Screening, Mult-disciplinary, Referral

B6-03

CHARACTERIZATION OF THE CONTROLLED CORTICAL IMPACT BRAIN INJURY MODEL BASED ON LONGITUDINAL MONITORING BY FDG-PET

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PET with ^{18}F-FDG is a sensitive, non-invasive imaging technique for mapping cerebral metabolism in both animals and humans. The aim of this study was to longitudinally evaluate FDG-PET as a biomarker of injury following controlled cortical impact (CCI) brain injury at mild, moderate, and severe injury levels in rats. Male Sprague Dawley rats (n = 40, 250–300 g) were categorized as injured (n = 24), sham with craniotomy (n = 8) or naïve (n = 8). Injured animals were subjected to a mild (n = 8), moderate (n = 8) or severe (n = 8) controlled cortical impact (CCI) injury. PET-FDG imaging was performed prior to injury and at 3–6 hours, 1, 3, 7, 10 and 20 days post-injury. Whole brain normalization and two-way ANOVA with repeated measures was used to evaluate group differences for 14 brain regions. Significant group differences were identified in the basal ganglia, thalamus, amygdala, cerebellum, cortex, hypothalamus, and white matter. For these regions, PET detected significant group differences at several time points with considerable effects at days 3 and 7. More specifically, decreased FDG uptake was observed in the basal ganglia and amygdala at days 3 and 7, and in the cerebellum at 3–6 hr and day 3, and an increase was observed for the corpus callosum at days 3 and 7. FDG-PET could detect differences between moderate and severe injuries compared to controls in the basal ganglia, amygdala, and cerebellum. In addition, FDG-PET detected decreases at day 3 after mild TBI. Atlas-based analysis of PET is sensitive to changes in regional FDG uptake at multiple time points and severity levels of CCI. Future work includes the analysis of left and right hemisphere data and correlation with behavioral and pathological data.

Keywords: PET, CCI, FDG

B6-04

KINETICS OF TRAUMATIC MENINGEAL INJURY USING DYNAMIC CONTRAST ENHANCED FLUID ATTENUATED INVERSION RECOVERY IMAGING

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Objectives: Traumatic Meningeal Injury (TMI) appears as enhancement of the meninges on post-contrast fluid attenuated inversion recovery (FLAIR) MRI in patients with suspected acute TBI. It is unknown whether the enhancement spreads from sites of focal injury or occurs diffusely within the meninges. Here we use dynamic contrast enhanced (DCE) FLAIR imaging to assess the kinetic properties of meningeal enhancement.

Methods: Patients presenting to a Level-2 trauma center were imaged on a 3T MRI within 96 hours of head injury. Subjects received a standardized research MRI exam consisting of a single FLAIR scan prior to single dose Gd-DPTA injection followed by four consecutive FLAIR scans spanning five minutes immediately after injection. A subpopulation of patients exhibiting TMI also received two additional FLAIR scans 25 and 45 minutes after injection. TMI was assessed visually by consensus of two raters blinded to time since injection, by region of interest analysis, and by voxel-based mapping.

Results: Of the 23 patients enrolled, 18 (78%) were positive for TMI, 16 (70%) showed an increase in enhancement between 2 and 5 minutes post-contrast, and four of six patients between 5 and 45 minutes post-contrast. Region of interest analysis of the area of greatest enhancement showed a two-fold increase in signal intensity in the meninges compared with brain parenchyma. Signal enhancement increased rapidly during the first few minutes with a median kinetic half-life of 1 minute (tau = 1.47 min).

Conclusion: Leakage of contrast in TMI occurs on a time-scale of < 10 min, and persists for at least the next 45 minutes with minimal change. Voxel-based mapping is needed to better describe spatial variations in uptake rate.

Keywords: TBI, DCE FLAIR MRI, Meninges, Traumatic Meningeal Injury, Kinetics, Blood Brain Barrier

B6-05

SHEAR SHOCK WAVE DEVELOPMENT IN NEUROLOGICAL TISSUES

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Non-classical interactions of shock waves with biologicals underline implications to traumatic brain injuries and diffuse axonal injuries. Injury patterns in blunt or blast induced neurotrauma are inconsistent with commonly held etiologies, like those based on relative motion. In high rate loading scenarios, where nonlinear effects dominate, interaction of shear shocks with soft tissues presents a compelling alternative to current hypotheses on injury mechanisms. When applied pressure is sufficiently high, low shear elasticity of brain allows nonlinear waveform distortion to produce shock fronts and accumulate highly localized stresses. Violent gradients in shear shock waves can tear and damage neurons as well as change estimates of damage at the brain skull interface. Nonlinear viscoelastic wave propagation in brain tissue was studied experimentally using high frame rate ultrasound and high speed video imaging. Parameters important to incipient shear shock formation were characterized. Tissue phantoms were created to examine effects of material properties (sound speed, nonlinearity, dispersion) and for *in vitro* cadaveric porcine brain imaging, layered construction allowed embedding of whole brain samples in gelatin. 128-channel radiofrequency data was collected at up to 10,000 fps, under shear loading conditions delivered by a vibration generator. Frequency, strain, and strain rate sweep tests were performed parametrically. B-mode image stacks were compiled into full-field displacement films using an adaptive displacement estimation algorithm. We complimented ultrasound data with high speed video which was used to capture external finite deformation of the gelatin/brain phantom during shear shock loading, at up to 20,000 fps with full resolution. External deformation was quantified with edge tracking in image processing software. For linear shear wave inputs, we showed shear shock wave behavior in the brain. In realistic, physiological range, (50–500 Hz and 10–100 Gs) we confirmed cubic nonlinear distortion and shock formation by third order harmonics in frequency content. We characterized the minimum requirements for shock front development and showed with neuroimaging techniques, the potential devastating cases of shock damage to brain tissue.

Keywords: Traumatic Brain Injury, Shear Shock, Ultrasound Imaging, High Speed Video

B6-06

CLINICAL UTILITY OF OUTPATIENT FOLLOW-UP COMPUTED TOMOGRAPHY IN A TRAUMATIC SUBDURAL HEMATOMA POPULATION

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Introduction: Following evaluation and/or treatment in a hospital setting, many patients with diagnosed traumatic subdural hematomas (SDH) are routinely seen in follow-up with a repeat computed tomography of the head (HCT) to assess for further progression of the lesion, regardless of clinical exam findings. This study aims to determine the clinical utility of additional routine HCT scans of brain trauma patients presenting with SDH on initial HCT.

Methods: A retrospective, single-center review of 319 traumatic SDH patients was performed at IU Health Methodist Hospital in Indianapolis from February 2007 to May 2012.

Results: Of 319 isolated traumatic SDH patients seen at a median follow-up of 50 days, follow up HCT revealed worsened findings in 8 (2.5%). 69 patients underwent further follow-up with additional HCT after the initial follow-up visit, with 11 of them suffering neurological decline. However, none of those who declined neurologically had worsened imaging findings. Surgical intervention was undertaken in only one patient who suffered neurologic decline. One patient underwent surgery based on worsened HCT without physical exam evidence of neurologic decline.

Discussion: Routine outpatient follow-up HCT poorly correlated with clinical decline and was not predictive of further surgical intervention. In our series, only one patient required surgical intervention based on the results of the CT, and one patient underwent surgery despite an unchanged CT. Additionally, there was no association between neurologic decline and worsening head CT findings. Based on these results, our institution now performs follow-up HCT on a patient-by-patient basis, and not routinely.

Conclusions: Routine outpatient follow-up HCT for traumatic SDH is poorly predictive of neurological decline or need for surgical intervention, and therefore should not be utilized.

Keywords: Computed Tomography, Subdural Hematoma, outpatient follow-up

B6-07

PET IMAGING OF α7 NICOTINIC ACETYLCHOLINE RECEPTORS IN A RAT MODEL OF TRAUMATIC BRAIN INJURY

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There is evidence that the α7 subtype of nicotinic acetylcholine receptors (α7-nAChR) plays a role in the physiology of acute brain injury, with growing evidence for its role in traumatic brain injury (TBI). We have developed a novel positron-emission tomography (PET) radiotracer ([18F]ASEM) that is highly specific and selective for distribution of α7-nAChR in brain. The main objective was to evaluate [18F]ASEM for imaging of α7-nAChR binding in a rat model of TBI. PET imaging and ex vivo biodistribution experiments were performed in a controlled cortical impact (CCI) rat model. The binding potential was calculated as BP_{ND} = (regional uptake/cerebellum) - 1. The following times after TBI were evaluated: 1, 3, 7 and 26 days. Sham-operated animals and uninjured control animals were compared with CCI animals (n = 5/group). Findings were correlated with staining of α7-nAChR's (rabbit anti-α7-nAChR antibody) in brain tissue. In the biodistribution

experiments, a significant reduction of BP_{ND} was observed on days 1 and 3 (up to 30–50%) in CCI rats, but there was no significant difference on days 7 and 26. A similar reduction of α7-nAChR binding on days 1 and 3 and recovery on days 7 and 25 was seen in the PET experiments. Evaluation of the cortical tissue demonstrated that neuronal α7-nAChR's are present in the sham, but are reduced in the ipsilateral hemisphere after CCI. In conclusion, there is significant reduction in expression of α7-nAChR's early (1d, 3d) after TBI, as measured by PET imaging, biodistribution, and immunohistochemistry. Validation of this non-invasive (PET) imaging of α7-nAChR binding after TBI in preclinical models will facilitate understanding of the pathogenesis of TBI, and could lead to clinical translation for diagnosis, prognosis and drug development after human TBI.

Keywords: nicotinic acetylcholine receptor

B6-08

DECREASED CEREBRAL BLOOD FLOW IS ASSOCIATED WITH WORSE COGNITIVE OUTCOME AFTER REPETITIVE CONCUSSIONS IN MICE

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Objectives: Repetitive concussions may result in long-term cognitive deficits that might be mitigated by adequate rest intervals between injuries. However, biomarkers of safe rest intervals remain undefined. Decreased cerebral blood flow (CBF) may be one such physiological biomarker. Using a mouse closed head injury (CHI) model of human concussion and diffuse correlation spectroscopy, we explored the effects of single and repetitive CHI on cortical CBF index and cognitive outcome.

Methods: Mice under isoflurane anesthesia were subjected to CHI by weight drop (54 g, 38 in drop height). Sham-injured controls received anesthesia alone. CBF was assessed at various times before and after CHI by diffuse correlation spectroscopy. Cognitive function was assessed after the final CHI using a version of the Morris water maze (MWM).

Results: After a single CHI, CBF was reduced by $35 \pm 4\%$ at 4 h and returned to pre-injury levels by 24 h. After 5 CHI spaced 1 day apart, CBF was reduced from pre-injury levels 4 h after each injury by approximately 20% but returned to pre-injury levels by 72 h after the final CHI and remained at pre-injury levels after 2.5 weeks. A single CHI did not induce MWM deficits, however, repetitive CHI led to significant deficits compared to sham ($p < 0.001$). After repetitive CHI, lower CBF measured both pre-injury and 4 hours after the third CHI was associated with worse performance in the MWM ($p < 0.01$). Similar relationships were not observed between cognitive deficits and CBF measured 4h, 72h, or 2.5 weeks after the final CHI.

Conclusions: Closed head injuries sustained by mice result in transient decreases in cortical CBF. Decreased cortical CBF may be a marker of an acute vulnerable period in which further injuries lead to long-term cognitive deficits. Diffuse correlation spectroscopy is a promising tool to interrogate the relationship between concussions and return to play interval in preclinical models as well as concussed patients.

Keywords: Concussion, diffuse correlation spectroscopy, cerebral blood flow, mice

B6-09

MRI FINDINGS IN ACUTE TBI: INTER-RATER RELIABILITY USING NIH COMMON DATA ELEMENTS

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Objective: The NIH-sponsored Common Data Elements (CDE) for Traumatic Brain Injury effort was designed to standardize data collected across centers to facilitate pooling of data and better-powered clinical studies. A standard dictionary of terms applied to specific pathoanatomic lesions seen on CT or MRI was published, encompassing lesions seen in all ages of patients from infancy through maturity.[1] MRI has advantages in children, involving no radiation exposure and providing improved sensitivity for many parenchymal lesions. We reviewed a series of acute MRI's obtained on children treated for TBI in our Pediatric Intensive Care Unit to measure inter-rater reliability of injury characterization using the CDE imaging dictionary.

Methods: 79 consecutive children treated for TBI in our Pediatric Intensive Care Unit undergoing early brain MRI were identified. Using the CDE neuroimaging definitions dictionary, the initial MRI was assessed and scored by two independent reviewers without knowledge of clinical factors or other imaging results (e.g., CT). After an initial practice set, 20 MRI's were scored independently and results compared. Scores included ''absent'', ''present'', or ''indeterminate'', and location for each lesion seen on each MRI. Inter-rater reliability was calculated using weighted kappa statistics.

Results: All patients (ages 1 month - 17 years) had MRI's within 2 days of injury. Agreement was ''perfect'' for cervicomedullary/brain stem lesion (1.00), ''very good'' for subdural hemorrhage (0.833), ''good'' for extra-axial hemorrhage (0.714), intraventricular hemorrhage (0.787), diffuse axonal injury (0.787), edema (0.655), midline shift (0.643), and hypoxia/ischemia (0.62), and ''moderate'' for epidural hematoma (0.588) and subarachnoid hemorrhage (0.559). Most differences occurred with very small (<1 cm) lesions. Skull fracture showed ''fair'' agreement (0.267).

Conclusions: MRI can characterize major acute TBI in children with high inter-rater reliability using the NIH Common Data Elements pathoanatomic definitions. These tools will enable reliable data collection and analysis across centers for comparative effectiveness and interventional trials for patients of all ages.

Keywords: Common Data Elements, Clinical trials, MRI, inter-rater reliability

[1] Arch Phys Med Rehabil. 2010 Nov;91(11):1661–1666.

B6-10

IN VIVO GLUCO-CEST MRI DETECTS METABOLIC CRISIS IN MILD TRAUMATIC BRAIN INJURY

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TBI results in an instant perturbation to cerebral glucose metabolism impairing longterm cognition. FDG-PET is the major imaging modality to track matabolic changes in brain. The drawbacks of PET

imaging, including image blurring, low resolution, radiation dose limitation and the increased FDG accumulation, may cause false-positive results in a longitudinal study. Here, we present an alternative MRI-based molecular imaging, named chemical exchange saturation transfer(CEST)-MRI, to detect the glucose metabolism without the need for a radioisotope. Our results indicate that glucose CEST-MRI(glucoCEST) could be another sensitive molecular imaging to detect metabolism in brain trauma.

A phantom experiment was first conducted including five glucose concentrations close to that of the living tissues(2 mM ~ 10 mM). Female SD rats(n = 6) were scanned for baseline, 1, 8, 16, 24 and 48 days-post-injury(DPI). glucoCEST were acquired using a Bruker 9.4T scanner (TR 3.5 s, TE 11.5 ms, resolution 200 μm, magnetization transfer(MT) pulse 2 μT/2s. MT-offset frequences($\Delta\omega$) were −2 kHz ~ +2 kHz with 100 Hz stepping(glucose at 1.2 ppm, 2.1 ppm, 2.9 ppm). MTR-asymmetry(MTRasym) derived from the glucoCEST data was applied to detect the glucose concentration. One-way ANOVA with repeated measures was performed by Prism.

MTRasym generated clear contrast in the glucose phantom and showed a linear relation to glucose concentrations. MTRasym maps clearly distinguished levels of metabolism between cerebral structures and exhibited temporospatial distributions of glucose in the injured brains. The glucose metabolism significantly decreased 40%($p < 0.01$) in the injured cerebral cortex at 1DPI and progressive decreased to 16DPI. The glucose metabolism then slightly increased and reached 67% of that of the baseline in 48DPI.

Energy supply and consumption is crucial to salvage the traumatized tissue. This study shows that glucose largely decreased after TBI and persisted chronically. The widespread hypometabolic changes affect the brain functions in learning and memory resulting in cerebral atrophy. glucoCEST delivers results comparable to previous PET studies yet delivers better image quality higher image resolution and sensitivity. glucoCEST could provide the window for effective treatments to increase the survival of traumatized tissue.

Keywords: glucose metabolic disorders, in vivo, glucoCEST

B6-11

MICROHEMORRHAGE IS NOT FOREVER: CROSS-SECTIONAL ANALYSIS INDICATES RESOLUTION OVER EXTENDED FOLLOW UP INTERVALS

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Objective: To determine whether or not traumatic microhemorrhage persists indefinitely, we evaluated microhemorrhage burden in two cohorts of patients with severe brain injuries; i) within 1 year of injury and ii) greater than 10 years post injury.

Methods: Traumatic brain injury (TBI) patients (n = 125) evaluated and imaged at NIH for the CNRM (Center for Neuroscience and Regenerative Medicine) were retrospectively reviewed to identify two cohorts of patients with severe TBI: an ''early'' cohort (evaluated < 1 y from injury), and a ''late'' cohort (evaluated > 10 y from injury. Because the distant time from injury in the ''late'' cohort precluded accurate documentation of severity according to DOD/VA criteria, we used loss of consciousness (LOC) of greater than 24 hours and a GCS at presentation of less than 12 to qualify as severe.

Microhemorrhage burden (total lesion counts) were made by a single neuroradiologist (JAB) by marking microhemorrhages on susceptibility weighted images (Carestream PACS v 12.0). Values for age and microhemorrhage burden are reported as mean ± standard deviation, and statistical comparison was made using the Mann-Whitney U-test (MedCalc).

Results: For the ''early'' cohort, 8 patients were identified (time from injury 0.46 ± 0.37 y) and for the ''late'' cohort, 6 patients were identified (time from injury 28.0 ± 6.2 y). Similar to the ''early'' cohort, imaging findings in the late cohort confirmed significant brain trauma, including non-hemorrhagic signs of traumatic/diffuse axonal injury such as focal notching in the corpus callosum, encephalomalacia from prior contusion, and hemorrhagic sequelae of traumatic brain injury, such as superficial siderosis. However, significantly fewer microhemorrhages were present in the ''late'' cohort as compared with the ''early'' cohort (3 ± 6 vs 167 ± 133, $p = 0.012$).

Conclusion: In severe TBI, numerous microhemorrhages are often identified shortly after injury, but are virtually absent in patients evaluated many years after the injury. The precise time course of such resolution is the subject for longitudinal imaging studies.

Keywords: susceptibility weighted imaging, microhemorrhage, severe

B6-12

IMPROVED VISUALIZATION OF SUPERFICIAL HEMORRHAGE IN SUSCEPTIBILITY WEIGHTED IMAGES

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Objective: Minimum intensity projection (minIP) is used to display susceptibility weighted images (SWI) - allowing the observer to distinguish microhemorrhage from vessel. Unfortunately, low signal intensity of the skull projects into the thick slab of the minIP, masking superficial tissues near the skull base and convexities. Because superficial contusions are a common feature of TBI, we develop a method to allow minIP projection to ''see'' superficial tissues adjacent to the skull.

Methods: To prevent low intensity extraaxial voxels form projecting into the thick slab of the minIP, we develop a method to precisely mask the brain and assign high signal intensity to voxels outside the brain mask. First, the Brain Surface Extraction algorithm (Shattuck,2001) is applied to generate two brain masks, one that is slightly too small and one that is slightly too large. The rind of tissue between these two masks is then a rind containing both high signal intracranial tissues and low intensity voxels of the skull to be excluded from the minIP process. Next, a clustering algorithm identifies tissues within this rind to rejoins missing brain tissue into the mask.

SWI (0.65 mm isotropic) arbitrarily selected from our database of patients with TBI were examined with minIP using the original data and masked data using the new method.

Results: For the standard minIP, ~1% of brain volume was lost per 1 mm of slab thickness. So for a typical 15 mm minIP 15% of the brain volume is completely hidden from the radiologist. For the new method, the visible brain tissue in the minIP reconstruction was complete and independent of slab thickness. Superficial microhemorrhage and superficial veins could be visualized in all cases.

Conclusions: The proposed method represents a significant improvement in minIP visualization of SWI data, allowing for superficial brain tissues to be assessed, surface venous anatomy to be visualized, and larger slab thickness applied. This has the potential to facilitate the detection of microhemorrhage, particularly in superficial cortex.

Keywords: susceptibility weighted imaging, microhemorrhage, contusion

B6-13

CHRONIC NEUROINFLAMMATION ANALYSIS AFTER TRAUMATIC BRAIN INJURY USING TSPO-PET AND MRI IN MICE

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Background: Traumatic brain injury (TBI) not only results in an initial functional deficit, but also is frequently followed by chronic cognitive impairment. The mechanism of this pathology has yet to be fully understood and methods to accurately quantify of the progress of these chronic traumatic encepalopathies are eagerly desired.

Objective: To detect neuronal inflammation *in vivo* in the chronic phase after focal traumatic brain injury using positron emission tomography (PET) and 11.7T magnetic resonance imaging (MRI).

Methods: Adult male C57BL/6J mice (8–10 weeks-old) were inflicted with a single controlled cortical injury. At 1, 4, 7, 14, 21, 28, 42, 63 and 94 days after injury, translocator protein (TSPO)-PET screening was performed. In addition, conventional MRI (T1, T2, T2*) and magnetic resonance spectroscopy (MRS) were performed.

Results: TSPO uptake at the injured cortex almost vanished from 14 days post injury. In contrast, long-term TSPO uptake was observed at the ipsilateral subcortex. T2-weighted MRI only detected faint, low intensity areas of interest localized at the ipsilateral thalamus. MRS in the associated area showed that peaks corresponding to Choline, Myo-inositol, and Lactate were higher than those in the contralateral thalamus. The peak corresponding to N-acetyl Aspartate was lower. Together with histological findings, these changes are thought to be chronically activated glial cells and neuronal damage in the thalamus.

Conclusion: We first reported long-term neuroinflammation spreading to the thalamus after TBI using *in vivo* imaging, TSPO-PET and MRS. These noninvasive imaging device could prove useful in determining the role of chronic inflammation.

Keywords: TSPO, PET, MRI, chronic phase

B6-14

ACUTE TRAUMATIC INTRACRANIAL LESIONS INCREASE THE RISK OF CERVICAL SPINE INJURIES

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Objective: To study the concurrence of CT (computed tomography)-detectible cervical spine injuries (CSI) and traumatic brain injury (TBI). We hypothesized that CT-positive TBI patients would have a significantly higher risk of having a concurrent CSI compared to CT-negative TBIs.

Methods: This retrospective study included 3023 consecutive patients who underwent head CT due to an acute head injury (HI) at the Emergency Department of Tampere University Hospital (August 2010–July 2012), Tampere, Finland. The medical records of these patients were reviewed to identify the individuals whose cervical spine was CT-imaged due to a clinical suspicion of a CSI within one week post-HI. Clinical data as well as CT findings (head and cervical spine) were systematically collected.

Results: Of the whole sample (n = 3023), 19.2% (n = 579) had an acute CT-positive TBI. Subdural hematomas (67.2%, n = 389) and subarachnoid hemorrhages (48.7%, n = 282) were the most common findings on head CT. The average age of the patients was 55.0 years (SD = 24.0 years) and 56.4% (n = 1705) were male. Car accidents 9.7% (n = 294) and falls 63.5% (n = 1921) were the most frequent injury mechanisms. Of the whole sample (n = 3023), 36.1% (n = 1091) underwent cervical spine CT within one week post-HI. On cervical CT, CSI (C0-CVII: fracture, dislocation, subluxation) was found in 2.5% (n = 77) of the patients. Altogether, 101 fractured vertebrae and 5 separate ligament injuries were detected. CII (0.8%, n = 23) was the most commonly injured vertebra. The patients with acute traumatic intracranial lesions had significantly (Pearson chi-square, $p = 0.001$; OR = 2.206) more CSIs (4.5%, n = 26) compared to head CT-negative patients (2.1%, n = 51). When the associations between CT-positive TBIs, cervical spine fractures and dislocation/subluxation were analyzed separately, only fractures were related to intracranial lesions ($p = 0.001$, OR = 2.206).

Conclusions: Head trauma patients with acute intracranial lesions on CT have a twofold risk of CSI in comparison to patients with a CT-negative head injury. CSI should be always acknowledged when treating CT-positive TBI patients. CT-imaging of the cervical spine in case of CT-positive TBI is recommended based on these findings.

Keywords: Traumatic brain injury, Cervical spine injury, Emergency assessment, Computed tomography, Head injury

B6-15

DIFFUSION MR IMAGING REVEALS ABNORMALITIES IN THE CORPUS CALLOSUM AFTER SINGLE TBI VERSUS OVERLYING CORTEX AFTER REPETITIVE TBI

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Non-invasive detection of brain abnormalities from single and repetitive mild traumatic brain injury (TBI) is important for evaluation of the acute through chronic effects of impact-acceleration head injuries. Magnetic resonance imaging (MRI) is beginning to reveal findings in mild TBI patients that are not detected with conventional imaging. This MRI study used diffusion tensor imaging (DTI) to evaluate longitudinal changes in both the corpus callosum and the overlying cortical gray matter after single and repetitive impact injuries in adult male C57BL/6 mice. For single TBI (sTBI), mice had a scalp incision to expose the skull and received a stereotaxically controlled impact (3 mm tip) at bregma (1.5 mm depth; 4.0 m/sec; 100 msec dwell time). For repetitive TBI (rTBI), mice received a milder impact (1.0 mm depth; 4.0 m/sec; 200 msec dwell time) onto the scalp over bregma each day for 5 days. Sham mice were run in parallel but without impact. T2-weighted MRI and DTI scans were performed at baseline and at 3, 6, and 42 days post-TBI/sham. Fractional anisotropy (FA) values were significantly decreased in the corpus callosum after sTBI, but not rTBI. Histological analysis of the corpus callosum confirmed less axon damage, astrogliosis, and

microglial activation in the rTBI model. Conversely, cortical regions had reduced axial diffusivity (AD) in the rTBI mice but not in sTBI mice. Respective DTI changes, in the corpus callosum after sTBI and in the cortex after rTBI, persisted through 42 days. These findings demonstrate that evaluation of mild rTBI should include region-of-interest analysis in the cerebral cortex and could be missed with widely used approaches for DTI analysis that are confined to white matter tracts. Funded by the DoD in the Center for Neuroscience and Regenerative Medicine.

Keywords: diffusion mri, mouse TBI model, repeat injury, cortical changes

B6-16

QUANTITATIVE WHITE MATTER ANALYSIS WITH HIGH DEFINITION FIBER TRACKING PREDICTS NEUROPSYCHOLOGICAL TEST PERFORMANCE IN CHRONIC TBI

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Objective: White matter injury is hypothesized to underlie the cognitive consequences of TBI. The current study correlated neuropsychological test performance with spatial properties of MR-based advanced diffusion tractography in chronic TBI and healthy control subjects.

Methods: Diffusion spectrum imaging data were acquired and processed for white matter tractography in a High Definition Fiber Tracking (HDFT) pipeline. All participants in both chronic TBI (N = 22 injured > 3 mo. before enrollment, 18 male, mean age = 38) and healthy control (N = 15, 8 male, mean age = 31) groups completed a neuropsychological test battery including TrailsAB, CVLT, WAIS-IV PSI, ANAM, and COWAT.

Results: In the chronic TBI group, HDFT metrics of symmetry (left-right homologue correlation, in X/Y/Z dimensions) and spread (proportion of voxels contacted in left and right hemispheres) were significantly correlated with neuropsychological tests across a range of cognitive functions. Correcting all tests for False Discovery Rate, within the TBI sample, verbal recall (CVLT) was positively correlated with Arcuate asymmetry, (Y dimension $r = 0.53$, $p = 0.01$) and Genu spread, (right hemisphere $r = 0.64$, $p < 0.01$), among others. PSI was correlated with Corona Radiata asymmetry (Y dimension $r = 0.61$, $p < 0.01$) and Genu spread (left hemisphere $r = 0.51$, $p = 0.04$). Trails A was positively correlated with Cingulum asymmetry (Y dimension $r = 0.48$, $p = 0.03$) and FOF spread (right hemisphere $r = 0.57$, $p = 0.01$. Trails B was positively correlated with Corona Radiata asymmetry (Y dimension $r = 0.65$, $p < 0.01$) and Uncinate spread (left hemisphere $r = 0.52$, $p = 0.01$). In contrast, almost all correlations in the control sample were zero or negative.

Conclusions: These results provide preliminary evidence that spatial white matter properties on MR-based diffusion spectrum imaging may be more informative in capturing impairment in behavioral performance following TBI than in capturing normal variability.

Keywords: DTI, TBI, neuropsychology, Fiber Tracking

B6-17

THE TYPE AND LOCATION OF INTRACRANIAL ABNORMALITIES FOLLOWING MILD TRAUMATIC BRAIN INJURY

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Background: Following mild traumatic brain injury (MTBI), head CT is used to identify gross structural brain damage and aid decision making on emergency treatment. Our objective was to describe the type and location of both acute and pre-existing intracranial abnormalities of patients who sustained head trauma and underwent computed tomography. Additionally, we investigated whether chronic cerebral lesions detectable with CT predispose to acute traumatic intracranial lesions.

Methods: The study population included all consecutive patients who underwent head CT due to acute head injury (n = 3,023; average age = 55.0 years, SD = 24.0; male = 56.4%) at the emergency department of Tampere University Hospital between August 2010 and July 2012. A neuroradiologist interpreted all the CT scans. The cohort was divided into two groups according the TBI severity: (i) mild TBI (n = 1,970) and (ii) moderate-severe TBI (n = 370).

Results: Pre-existing chronic lesions were present in 35.5% of MTBI and 30.3% of moderate-severe patients. In the MTBI group and the moderate-severe TBI group, the most common pre-existing chronic lesions were microangiopathy and generalized atrophy. Acute traumatic lesions were found in 19.9% of MTBI and 64.6% of moderate-severe TBI patients. In the MTBI group and the moderate-severe TBI group, the most common traumatic lesions were subdural hematomas (11.8% and 43.8%), subarachnoid hemorrhages (7.1% and 38.6), and contusions (5.6% and 30.2%). Pre-existing traumatic lesions (previous contusions and hemorrhages) were associated with contusions (risk ratio 1.21, $p < 0.001$), subdural hematomas (RR 1.14, $p = 0.011$), any traumatic lesion (RR 1.17, $p = 0.02$) and multiple traumatic lesions (RR 1.15, $p = 0.003$).

Conclusions: A significant number of TBI patients have chronic lesions found in CT imaging. One in five MTBI patients have an acute traumatic CT finding. Patients, who have chronic trauma-related lesions seem to be more likely to sustain acute traumatic lesions.

Keywords: Head injury, CT imaging, Comorbidity, Patient recruitment, Mild traumatic brain injury

B6-18

PET IMAGING WITH PITTSBURGH COMPOUND B OF AMYLOID DEPOSITION IN WHITE MATTER IN CHRONIC TBI

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Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disorder linked to repetitive TBI and diagnosed by autopsy. This current study explores PET imaging with Pittsburgh Compound B (PiB) to identify amyloid pathology in chronic TBI.

Methods: [11C]PiB PET data (8 male TBI subjects, mean age 47) were compared to 15 healthy adults (7 males, mean age 59). PiB SUVR images were calculated with cerebellar grey matter (GM) as reference and aligned to diffusion data by registering to T1 MR sequences. High b-value diffusion imaging was processed in a High Definition Fiber Tracking (HDFT) pipeline. Cortical segmentation was performed using Freesurfer; labels were transferred to diffusion space using FSL software. We performed two hierarchical regressions to analyze diencephalic white matter (WM) regions: 1) regional corpus callosum (CC) PiB SUVR treating TBI status (TBI/Control), age, and region and their 2-way interactions as fixed effects; 2) voxel-level WM PiB SUVR within TBI subjects, treating diffusion gFA, region, and interaction as fixed effects.

Results: One participant was classified as PiB-positive (elevated uptake in GM ROIs for Alzheimer's Disease). PET PiB SUVR was reduced in TBI subjects in Anterior and Mid-Anterior CC regions ($p = .03$ & $p < .01$). Within TBI subjects, higher gFA significantly predicted higher PiB SUVR at a voxel level in 3/5 CC regions and in cerebral WM (all $p < .01$). PiB SUVR within TBI subjects was greatest in Anterior and Mid-Anterior regions of CC (ß(anterior) = 0.45, ß(mid-anterior) = 0.32).

Conclusion: Our preliminary analysis found changes in PiB uptake in chronic TBI in the corpus callosum, a known area of vulnerability to TBI damage, in the absence of the typical gray matter PiB deposition seen in Alzheimer's Disease. These are promising pilot results in the search for an *in vivo* neuroimaging biomarker panel for CTE.

Keywords: Amyloid, White matter, Chronic TBI

B6-19

LONGITUDINAL CHANGES IN REGIONAL BRAIN VOLUME IN PEDIATRIC TBI: PRELIMINARY ANALYSES

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Traumatic brain injury (TBI) can cause widespread and prolonged brain degeneration. This is especially damaging in young patients as it may delay or alter brain development. We present preliminary longitudinal analyses of regional brain volume change, assessed by tensor-based morphometry (TBM) in pediatric moderate/severe TBI. We assessed participants in the post-acute phase (1–6 months post injury) and chronic phases (13–19 months post injury). We examined 40 participants: 15 with TBI (mean age at T2 = 15.7, 4 female) and 25 controls (mean age at T2 = 16.3, 10 female). We used the TBM protocol developed by our lab to generate Jacobian determinant maps describing the displacement between T1 and T2 within subject. We then ran a voxel-wise linear regression testing for group differences in these longitudinal volume changes, covarying for age, sex, scanner, and intracranial volume (ICV). Results were corrected for multiple comparisons using searchlight FDR across the whole brain ($q < 0.05$). We found significant differences in the genu, mid body, and splenium of the corpus callosum – areas where the control group showed little to no change over time, while the TBI group showed atrophy. We also found significant differences in a large cluster between hemispheres spanning the frontal and parietal cortices, indicating tissue contraction and CSF expansion. Our results indicate continued, progressive tissue changes in the first year post-injury. Whether these changes indicate progressive damage, or a natural progression of injury and recovery is a topic for future investigation.

Keywords: traumatic brain injury, pediatric, tensor based morphometry, MRI, volume, longitudinal

B6-20

AMYLOID PLAQUES ARE INCREASED IN THE BRAIN OF TBI SURVIVORS AT 1, 12, AND 24 MONTHS AFTER INJURY

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Background: Traumatic brain injury (TBI) is a well recognized risk factor for Alzheimer's disease (AD). With respect to amyloid deposition, there is little published data regarding the timing, location, and deposition rate of amyloid in the brain after TBI, and no longitudinal studies are available.

Objective: The primary objective of this study was to conduct serial ^{18}F-AV-45 (florbetapir F18) positron emission tomography (PET) imaging in severe TBI subjects after injury.

Methods: Serial florbetapir F18 PET imaging was conducted in 2 individuals with a severe TBI at 1, 12, and 24 months after injury. A total of 12 brain regions were surveyed for amyloid accumulation.

Results: Subject 1, was a 50 year old male who experienced a severe TBI with moderate-to-good cognitive/functional outcomes (GOSE = 7). An increase in amyloid (as indicated by standard uptake value ratios [SUVR]) was observed in the hippocampus (+16%, left; +12%, right) and caudate nucleus (+14%, left; +18%, right). At year 2, subject 1 complained of severe memory deficits, which was captured on the Rivermead symptom list. The lone affected brain region at year 2 was the right hippocampus (15% increase of amyloid). Subject 2 was a 37 year old male who suffered a severe TBI and a poor outcome (GOSE = 6). An increase of amyloid in the left anterior (+39%) and posterior (+20%) putamen was observed at year 1. Also, a reduction of amyloid was observed in the precuneus at the 12 (-19%) and 24 (-11%) month time-points.

Conclusions: Compared to SUVRs at 1 month, amyloid clearance and accumulated was observed at all time-points. Longitudinal imaging conducted here suggests that florbetapir F18 PET imaging may be useful in monitoring amyloid dynamics within brain regions following severe TBI and may be predictive of cognitive deficits.

Keywords: amyloid, TBI, florbetapir F18, PET imaging

B6-21

DIFFUSION TENSOR IMAGING ANALYSIS OF MILD TRAUMATIC BRAIN INJURY

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Mild traumatic brain injury (mTBI) is a rising epidemic affecting millions of people each year. Our understanding of mTBI is still in its infancy and to gain a greater understanding relevant animal models should replicate many of the features seen in human mTBI. These include changes to diffusion tensor imaging (DTI) parameters, the absence of anatomical lesions on conventional neuroimaging, and changes to neurobehavioral outcomes. These changes are transient in majority of the mTBI victims. The Maryland Model of TBI causes the anterior-posterior plus sagittal rotational acceleration of the brain frequently observed with motor vehicle and sports related TBI injuries without skull fracture (Kilbourne et al., 2009). The goal of our study was to characterize longitudinal pathophysiological changes following a single mTBI using magnetic resonance imaging (MRI), behavioral assays, and histology. On DTI we observed a significant difference in fractional anisotropy (FA) and longitudinal and radial diffusivities in the internal capsule 72 hours after injury compared to baseline measures (n = 11). A significant difference in longitudinal diffusivity was also observed in the genu of the corpus callosum also at 72 hours compared to baseline measures. The exploratory activity computerized activity box showed significant decrease in the ambulatory distance, average velocity, stereotypic counts, and vertical counts compared to baseline measures at 72 hours. Histological examination of the mTBI brain sections indicated a significant decrease in the expression of myelin basic protein in the internal capsule. A significant increase in the number of apoptotic cells was observed by caspase-3 labeling in these brains as well as compromise of the blood brain barrier by immunoglobulin-G detection. The changes with DTI and neurobehavioral outcomes were only observed during the acute phase of injury, similar to what was observed in human mTBI (Narayana et al. 2015). Thus this experimental TBI replicates the observations in human mTBI and can be used to investigate the long-term effects of mTBI.

Keywords: fractional anisotropy, longitudinal and radial diffusivities, neurobehavioral

B6-22

ACUTE CHANGES IN FDG PET AFTER SINGLE AND REPEAT MTBI IN RATS CORRELATE WITH CLINICALLY RELEVANT SYMPTOMS OF CONCUSSION

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Mild traumatic brain injury (mTBI) can lead to immediate symptoms (headache, dizziness, confusion, loss of consciousness) but lack gross pathology on computerized tomography (CT). Most patients recover within 10 days but a minority have continued deficits. Change in 18F-fluorodeoxyglucose (FDG) positron emission topography (PET) has been suggested as a potential prognostic indicator of this minority. Here we evaluated FDG and CT 24 hr post-injury in a rat concussion model using single and repeat projectile impacts (sPCI, rPCI) to the right cortex. Unlike other mTBI injury models this model lacks any gross pathology/injury. Post-injury, animals were evaluated for righting reflex (RR; immediately) and gait analysis (2 hr). Injured animals were compared to their respective single (sSham) or repeat (rSham) sham controls (equivalent anesthesia, no impact). All rats were negative for CT findings including skull fracture. Following sPCI, RR time was increased and gait analysis showed decreased swing speed compared to sSham; FDG levels were significantly increased in right olfactory bulb (OB). rPCI also showed increased RR time and decreased limb swing speed compared to rSham; OB FDG levels were increased. In addition, following rPCI FDG levels were increased in right cortex and decreased in left hypothalamus. Increases in energy utilization may indicate cells in these regions have initiated recovery processes rather than committing to cell death. Increased FDG levels in OB correlated with increased RR and decreased swing speed, suggesting this area may be an acute marker of injury severity in the absence of gross lesions or positive CT. Although not well studied, damage to the OB and smell dysfunction have been reported following mTBI. Given the proximity of the OB to the skull, this area may be particularly sensitive to coup counter coup injury following concussion. Ongoing studies will determine whether FDG-PET alterations continue, or have prognostic value, for long-term deficits.

Keywords: Concussion, mTBI, PET, FDG

B6-23

SOFTWARE TOOL FOR LOADING TRAUMATIC BRAIN INJURY NEUROIMAGE DATA INTO AN EXTERNAL REPOSITORY

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Objective: Our overall objective is to load neuroimage data into an external data repository from a military population at the National Intrepid Center of Excellence (NICoE). NICoE has image data from a large number of chronic TBI subjects (N = 800). The Federal Interagency Traumatic Brain Injury Repository (FITBIR) is a database for sharing research data on TBI subjects and relating subjects across studies while protecting their privacy. The objective of this work is to create a software tool to facilitate transfer of data into the FITBIR repository, in order to increase accuracy and reduce operator time.

Methods: We created a Python software tool, FITBIR Import of Neuroimage Data (FIND), which takes a list of coded subject identification numbers, finds selected anonymized image data from our archive/processing pipeline, subject image database and extracts indexing metadata from these files and other coordinated databases. FIND builds an upload package of the image files and associated metadata for each subject and stores them in a FITBIR submission package. This upload package can be pushed through the FITBIR image submission preparation program which verifies our extracted metadata with the metadata stored in each image file, and generates a thumbnail image for FITBIR. The package is then validated and uploaded by the FITBIR submission tool.

Results: FIND successfully imported 40 full MRI datasets for 6 subjects, and made this task much simpler than available methods. It is being expanded to include PET data, to generate a thumbnail image for each image type, and to extract other useful metadata from DICOM files to give more control than allowed by the FITBIR image processing tool.

Conclusion: We have created a tool to automate and simplify the importation of large numbers of image files into FITBIR. We are making it available to other users via FITBIR. We have made FIND available to others through GitHub, a web-based software repository.

Keywords: Software, Database, Sharing, FITBIR, military, blast

B6-24

SHARED NEUROIMAGING DATA OF MILITARY AND BLAST TRAUMATIC BRAIN INJURY USING A DATA SHARING REPOSITORY

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Objective: We are sharing neuroimaging data (N = 300) through the Federal Interagency Traumatic Brain Injury Repository (FITBIR) so that academic researchers have access to our unique military population for secondary and meta-analysis.

Methods: Subjects receive two 45-minute scans on a GE Signa 750 3T MRI scanner with a 32-channel phased array head coil. This includes conventional structural volumetric brain imaging of T1, T2, flair, and post-contrast imaging. Subjects also receive perfusion, MR spectroscopy, susceptibility-weighted, diffusion tensor, and both resting and task-based functional imaging. Subjects also elect to undergo a brain CT scan and PET scan using F-18 fluorodeoxyglucose. In addition to demographic and prior injury information, the SF-36 Health Survey, Neurobehavioral Symptom Inventory (NSI), Combat Exposure Scale (CES), and PTSD Checklist (PCL-C) are shared. We use a custom tool shared with FITBIR to submit these data. These data provide military-specific information that we hope spurs increased research on TBI in the military, and provide many of the same measures that are collected in civilian studies.

Results: We chose subsets of our neuroimaging subjects to share at an accelerated schedule (N = 300) to spur academic research in military TBI. These are curated into subsets ideal for resting-state and other modalities. These data are the first in FITBIR with CES, PET, spectroscopy, and annotated task-based fMRI data; we are working with FITBIR to develop methods to query these data. These data will be the first large military TBI dataset in FITBIR.

Conclusion: Researchers throughout the TBI community now have access to a large and diverse military clinical TBI population for secondary and meta-analysis. We anticipate that this will spur increased study of military and blast TBI at civilian research centers, and augment smaller research studies. While data currently being submitted to FITBIR have a long schedule for data sharing, we are making these datasets widely available within FITBIR for increased research in military TBI.

Keywords: database, FITBIR, neuroimaging, military, blast

B6-25

CONNECTOME-SCALE ASSESSMENT OF BRAIN NETWORK CONNECTIVITY IN MILD TRAUMATIC BRAIN INJURY

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Most mild traumatic brain injury (mTBI) patients have normal findings in clinical neuroimaging despite their constellation of clinical and neurocognitive symptoms after injury that significantly impact their quality of life. Mounting evidence suggests alterations in brain functional connectivity (FC). Identifying FC alterations on a large scale or connectome-scale can provide us a better understanding of the network substrates of brain injury, which can potentially assist physicians to select appropriate treatments. In this longitudinal study, FC of the brain has been evaluated on a large scale. Diffusion tensor and resting state functional magnetic resonance imaging (fMRI) data were acquired for 24 healthy subjects at two time points with a 6-weeks interval and 16 mTBI patients at acute and sub-acute stages at Detroit Receiving Hospital. A novel prediction framework was utilized to identify 358 network nodes, known as dense individualized common connectivity based cortical landmarks (DICCCOLs), distributed all across the whole brain. The location of each DICCCOL was identified based on the white matter fiber connection profile optimized from fiber tractography. Each DICCCOL preserves structural and functional properties across individuals with maximum group consistency. The longitudinal statistical analysis was performed using a mixed design analysis of variance (ANOVA) and Network-Based Statistic (NBS) to identify disrupted FCs, known as connectomic signatures. The group effect identified 258 FCs significantly affected in mTBI patients. All connectomic signatures showed increased FC in the patient group. These 258 connectomic signatures were further categorized using meta-analysis and a data-driven approach, called multiview spectral cluster analysis. Meta-analysis reveals that the interaction between ''Action'' and ''Cognition'' functional domains, specifically the interaction between ''Execution'' (from ''Action'') and ''Attention'' (from ''Cognition'') are affected the most. Categorizing connectomic signatures using a clustering approach identified that the general pattern of FC changes could be related to a Posterior-Anterior compensatory mechanism of the brain.

Keywords: Connectome, Functional connectivity, Large-scale brain networks, mild traumatic brain injury

B6-26

VALIDATION OF DUAL-INJECTION PERFUSION IMAGING: A PILOT STUDY

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Traumatic brain injury (TBI) could render deficits in cerebral blood flow and metabolism, measurable by advanced imaging techniques. Dynamic susceptibility contrast perfusion weighted imaging (DSC-PWI) suffers from blooming, clipping, and saturation effects in large vessels, which make of arterial input function (AIF) determination unreliable. To combat this, we have used a dual-injection method, in which 1/6 of the contrast dose is used to determine the AIF and the remaining 5/6 is used to visualize the perfusion in brain tissue. We compared cerebral blood flow (CBF) measurements to those from pseudo-continuous arterial spin labeling (pCASL), an MR method with good reliability, validated against positron emission tomography (PET). Two subjects underwent imaging with pCASL and DSC-PWI. DSC-PWI was performed twice (with 1/6 dose, then with 5/6). AIF was generated from the low-dose PWI scan, scaled up, and applied to the high dose data. The pcASL CBF maps were coregistered to these and regions of interest (ROIs) drawn, each in a single tissue type. The correlation coefficients of 0.85 and 0.63 show good correlation in large ROIs and slightly poorer correlation in the small ROIs, respectively. PWI analysis performed with only the high dose data and no AIF prediction showed a worse R^2 of 0.76 in the large ROIs. The improvement of R^2 between DSC-PWI and pCASL with the low-dose

AIF supports our plan to use this method in the future for traumatic brain injury studies. The loss of correlation in smaller ROIs is likely due to a lack of smoothing of the blood vessels with the higher resolution DSC-PWI; the standard deviation is much higher than in the pCASL data. In summary, the dual-injection DSC-PWI method provides a reliable, high resolution measurement of CBF, which could be useful in TBI.

Keywords: Cerebral blood flow, Perfusion weighted imaging, Arterial spin labeling, Validation

B7 Poster Session IV - Group B: Neuropathology

B7-01

CLINICOPATHOLOGICAL FINDINGS IN 100 FORMER NFL PLAYERS

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In 2008, a brain bank was created by Boston University School of Medicine, VA Boston, and Sports Legacy Institute to better understand the long-term effects of repetitive mild brain trauma (RBT). To date, 255 brains have been harvested from individuals exposed to RBT through sports, military service or other means, including 100 former National Football League (NFL) players. NFL players ranged in age from 23–98 yrs at death, mean 65 yrs: 76% Caucasian, 23% African American, 1% Pacific Islander. The mean age at first exposure to football: 12 yrs, mean total playing yrs: 17, mean yrs in the NFL: 7. 80 of the 84 (95%) neuropathologically analyzed were diagnosed with CTE (mean stage III (max IV)) using criteria (McKee, 2013) recently confirmed by the First NIH Consensus Conference to Define the Neuropathological Criteria for the Diagnosis of CTE, http://www.ninds.nih.gov/research/tbi/ReportFirstNIHConsensusConference.htm. Players with CTE played every position except kicker. 50 (63%) were diagnosed with pure CTE, 37% had co-morbid neurodegeneration. Of those with pure CTE, 2% had no symptoms (mean age at death 48 yrs). 20% presented with mixed behavioral and cognitive changes (mean onset: 45 yrs, age at death: 57 yrs), 48% presented with behavior and mood changes (mean onset: 39 yrs, age at death: 63 yrs), 24% presented with cognitive changes (mean onset: 56 yrs, age at death: 71 yrs). The overwhelming majority of this sample of former NFL players had at least stage II CTE. However, ascertainment bias is a recognized limitation of brain donor cohorts, even when inclusion criteria are based solely on exposure, and caution must be used in interpreting the high frequency of CTE in this sample. The precise clinicopathological characterization of this NFL cohort will provide valuable information to aid in the future detection, management, and treatment of CTE in living individuals.

Keywords: Trauma, Tau protein, Football, Sports

B7-02

EARLY CHRONIC TRAUMATIC ENCEPHALOPATHY IN YOUNG ATHLETES AFTER CONCUSSIVE HEAD INJURY AND A MOUSE MODEL OF IMPACT CONCUSSION

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The mechanisms by which head injury induces acute concussion and chronic sequelae are not known. We examined postmortem brains from young athletes after concussive head injury and found parenchymal contusion, myelinated axonopathy, microvasculopathy, neuroinflammation, neurodegeneration, and phosphorylated tauopathy consistent with early chronic traumatic encephalopathy (CTE). We developed a biofidelic mouse model of impact concussion that induces non-skull deforming head acceleration, acute concussion, and traumatic brain injury (TBI) in unanesthetized C57BL/6 mice. Impacted mice exhibited contralateral circling, limb weakness, locomotor abnormalities, and impaired balance that recapitulates human concussion. Neurological function rapidly returned to baseline, but markers of early CTE persisted long after recovery. Impact concussion induced blood-brain barrier disruption, neuroinflammation, impaired hippocampal axonal conduction, and defective long-term potentiation (LTP) of synaptic transmission in prefrontal cortex. Kinematic analysis revealed head acceleration sufficient to induce concussion, TBI, and CTE-linked pathology. Notably, concussion did not correlate with CTE markers or chronic sequelae. Concussion was observed following impact injury but not blast exposure under conditions of comparable head kinematics. Dynamic modeling revealed greater brain shear stress during impact compared to blast neurotrauma. These results indicate that while acute concussion and chronic sequelae may be triggered by the same insult, the pathophysiological responses underpinning these effects engage distinct mechanisms and time domains. Concussion per se is neither necessary nor sufficient to trigger acute brain injury and chronic sequelae, including CTE. These results suggest that the critical variable of clinical relevance is neurotrauma exposure (hits).

Keywords: chronic traumatic encephalopathy, traumatic brain injury, concussion, impact, blast, neurotrauma

B7-03

INJECTABLE FIDUCIAL MARKER IN MRI GUIDED PATHOLOGY OF BRAIN INJURY

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There has been growing interest in pathology underlying focal MRI abnormalities, such as traumatic microbleeds, in efforts to increase sensitivity of MRI based diagnosis. MRI has been used to guide sectioning of brain tissue, however co-localization of MRI and histology is not trivial. Here we introduce the use of an injectable fiducial marker combined with a 3D-printed structure for imaging and sectioning of the brain, to reduce ambiguity of MRI guided pathology. Acrylic paint containing iron oxide was chosen as an injectable fiducial. Two donated fixed specimens were used for this work; coronal sections to verify the fiducial, and whole brain for

localization and sectioning. To determine the stability of the fiducial, the coronal sections were injected and scanned with 3T MRI immediately after injections and 7-weeks post injections. A sample of injected tissue was extracted and H&E staining was performed to confirm the fiducial. The whole brain was imaged at 3T, following vacuum impregnation with fluorinated oil to eliminate air. The brain surface was generated from MR images and used to design a holder/slicer. A prototype holder/slicer for the whole-brain was printed. The injected fiducial was visible on 3T T2*-weighted MRI images. Histology results are pending. Additional examination confirmed that time did not impact the conspicuity of the fiducial. The two printer polymers introduced negligible artifact on MRI of the brain and air bubbles were absent following vacuum impregnation with fluorinated oil. Work continues on the whole brain to inject a targeted fiducial, detect it on MRI while in the holder/slicer, and use MRI to guide the sectioning and co-localization in histology. A fiducial marker and 3D-printing method for generating an individualized holder/slicer to aid in MRI guided pathology has been identified, and will be used to target specific pathology seen on in-vivo MRI in donated TBI specimens.

Keywords: MRI Guided Pathology, TBI, Fiducial

B7-04

LONG-TERM COGNITIVE DEFICITS INDUCED BY TRAUMATIC BRAIN INJURY IN RATS ARE EXAGGERATED BY PRE-EXPOSURE TO LIFE-THREATENING STRESS

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In the military, traumatic brain injury (TBI) is often sustained under extremely stressful circumstances. However, the influence of such stress on the outcome of TBI has been overlooked. Here, using a rat model, we aimed at determining if behavioral and cognitive outcomes after TBI are affected by prior exposure to life-threatening stress. Adult male Sprague-Dawley rats were stressed by exposure to predator odor 2-4-5-trimethyl-3-thiazoline (TMT) for 7 minutes or were exposed to water (WAT) instead of TMT; exposure was repeated 8 times at irregular intervals over a 2-week period. Two days after the last exposure, rats were subjected to either bilateral mild-to-moderate fluid percussion brain injury (LFP) or Sham surgery. In our 4 experimental groups (Sham-WAT, Sham-TMT, LFP-WAT, LFP-TMT), we measured motor activity and anxiety-like behaviors at 1, 2 and 6 weeks post-trauma, spatial learning and hippocampal long-term potentiation (LTP) at 1 month post-trauma, and basal activity and restraint-stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis at 2 months post-trauma. Compared with Sham-WAT rats, LFP-WAT rats exhibited transient signs of motor hyperactivity but no sign of anxiety at 1 week post-trauma, minor spatial learning and hippocampal LTP deficits, and, finally, lower basal activity of the HPA axis with slightly stronger reactivity to restraint-stress. Exposure to TMT had negligible effects on Sham rats, whereas it exaggerated all deficits observed in LFP rats except for motor hyperactivity. Hence, these data suggest that pre-exposure to stress can aggravate long-term deficits induced by TBI.

Keywords: TBI, animal model, stress, cognition, behavior

B7-05

NEUROMETABOLIC CONSEQUENCES OF REPEATED TBI

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Head injuries are a major public health concern for youth and adult athletes, members of the police and armed forces and the general public. In the US alone, each year approximately 1.4 million people are hospitalized with a traumatic brain injury. There is an innate conflict between an institutional desire to return individuals to the playing field or to duty following a TBI, and the need to protect these individuals from the catastrophic brain damage that can result from subsequent head injuries. The pathophysiology of TBI is complex, but involves diffuse axonal injury, frank neuronal death, inflammation, and persistent metabolic abnormalities. There is a consistent phenomenon across brain injury subtypes that the capacity for the brain to utilize energy (viz. glucose) is significantly modulated following injury. We recently reported that repeated injuries occurring close in time were associated with greater axonal degeneration, enhanced inflammatory responses, poorer functional outcomes, and alterations in central glucose utilization. In order to understand the metabolic determinants of this phenomenon we investigated the role of insulin, known both for its role in blood glucose regulation as well as being a potent neuroprotectant following CNS insults. There is mounting evidence that central insulin resistance and neuronal metabolic dysfunction are key components of neurodegenerative diseases and other neurological conditions. Here, we injured mice either once or twice and investigated *ex vivo* sensitivity to insulin. Insulin sensitivity, as assessed by Akt phosphorylation, was significantly reduced 48 hours after both single and repeated injuries. Importantly, by 7 days after injury, insulin sensitivity was restored in animals that were injured once, but not repeatedly. Ongoing work is investigating the molecular mechanisms and consequences of this phenomenon for recovery.

Keywords: Glucose Utilization, Insulin Sensitivity, Neurometabolics, Repeated TBI

B7-06

IMPROVEMENTS IN COGNITIVE FUNCTION FOLLOWING TRAUMATIC BRAIN INJURY VIA EIF2α PHOSPHORYLATION AND REDUCTION IN ER STRESS

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Memory deficits are often seen after an individual has suffered from a traumatic brain injury (TBI). Typically damage leading to these impairments involves structures such as the hippocampus. Subsequent to TBI there is a complex cascade of biochemical events that impact potential recovery. Endoplasmic reticulum (ER) stressors such as increased calcium levels, oxidative damage, and energy/glucose depletion have all been observed in the pathophysiology of TBI. In response to these events protein kinase RNA-like ER kinase (PERK) regulates protein synthesis (via phosphorylation of eIF2α). Administration of the FDA approved drug, guanabenz, has been demonstrated to increase eIF2α phosphorylation and decrease ER stress. In the current study, guanabenz (5.0 mg/kg) significantly reduced cortical contusion volume and lessened hippocampal cell damage.

Additionally, treatment with guanabenz reduced deficits in motor and vestibulomotor function, improved recognition memory, as well as, spatial learning and memory ability. Subjects treated with guanabenz also demonstrated better cognitive flexibility relative to their vehicle treated counter-parts. Intriguingly, delaying the start of treatment by 24 hours or reducing the dose to 0.5 mg/kg, resulted in many of the same beneficial effects. Because of the persistent nature of cognitive deficits following TBI there is a growing demand for effective treatments. The results of the current study further lend support to ER stress signaling being involved in TBI pathophysiology and that guanabenz may aid in improving cognitive deficits.

Keywords: ER Stress, Hippocampus, Traumatic Brain Injury, eIF2α, Learning and Memory, Recovery of Function

B7-07

EXPOSURE TO ANABOLIC ANDROGENIC STEROIDS DOES NOT EXACERBATE ACUTE POST-INJURY OUTCOMES IN MICE SUBJECTED TO REPETITIVE CONCUSSION

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Background: An unknown proportion of athletes with high concussion exposure develop chronic traumatic encephalopathy (CTE), a neurodegenerative disease characterized by altered mood, behavior and cognition, motor dysfunction and extensive deposition of phosphorylated tau. Factors that may modulate CTE risk are virtually unknown. Androgenic anabolic steroids (AAS) are performance-enhancing substances known to increase aggression and alter function of the gonadal hypothalamic pituitary axis. Whether systemic exposure of AAS increases the vulnerability of the brain to concussion is not known. Here we tested the hypothesis that AAS treatment would exacerbate aggression, neuroinflammation and/or tauopathy after repeated NFL-like concussion in mice.

Methods: Gonadally-intact, 8-week old male C56Bl/6 mice were treated with a cocktail of commonly used AAS (2.5 mg/kg each of: 17alpha-methyltestosterone, nandrolone and testosterone) or sesame oil vehicle for 7 weeks prior to receiving two NFL-like concussions spaced 24h apart using our previously described CHIMERA (Closed Head Impact Model of Engineered Rotational Acceleration) model of traumatic brain injury (TBI). Naïve mice received neither AAS cocktail nor sesame oil vehicle. Behavioral, biochemical and neuropathological outcomes were assessed up to 7 days post-TBI.

Results: Prior to repeated concussion, AAS-treated mice exhibited increased body and seminal vesicle weights, reduced testicular weight, and reduced latency to fight in the resident-intruder task of aggression. Compared to sham controls, mice subjected to TBI were impaired in several behavioral measures including loss of righting reflex, neurological severity score, accelerating rotarod performance, and thigmotaxis. Naïve and treated mice also displayed increased diffuse axonal pathology and white matter inflammation post-TBI. No significant treatment effect of AAS exposure on TBI phenotypes was observed in any outcome measure evaluated in this study.

Conclusions: Under our experimental conditions, exposure of wild-type male mice to AAS did not exacerbate any post-TBI outcome including behavior, diffuse axonal injury, inflammation or phosphorylation of murine tau.

Keywords: Chronic traumatic encephalopathy, Androgenic anabolic steroids, Sport concussion

B7-08

EVIDENCE OF BOTH BRAIN AND SPINAL CORD INJURY IN RATS EXPOSED TO EXPLOSIVE-DRIVEN PRIMARY BLAST

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The high prevalence of blast-related brain injury among military casualties of recent wars has led to an increasing number of studies focused on the vulnerability of brain to blast's ''primary'' mechanism of injury. Very little focus has been put on spinal cord's vulnerability, possibly because of lack of prominent specific symptoms. Balance impairment is increased after exposure to primary blast, but is generally ascribed to vestibular injury. The objective of our study was to evaluate the impact of primary blast on both brain and spinal cord. The neurobehavioral and neuropathological outcome was evaluated at several times following exposure of rats to explosive-driven primary blast. After hearing loss, gait impairment, as objectively measured on a Catwalk apparatus, represented the most significant behavioral outcome of blast exposure, peaking at 15 days for several parameters. The most prominent neuropathological feature was represented by blast-intensity dependent FD Neurosilver- and Fluoro-Jade B-marked neurodegeneration, evident between 7 and 28 days after exposure. Areas of astrocyte and microglia activation coincided almost exclusively with the areas of neurodegeneration. In brain, neurodegeneration was detectable in the visual pathways, cerebellum and medial lemniscus. Importantly, evidence of neurodegeneration was found at all levels in the spinal cord. It involved dorsal corticospinal tract, ventral and lateral funiculi, including the ventral medial fissure, lamina 8 area of the ventral horns (all levels), and postsynaptic dorsal column (cervical and thoracic levels). The second most prominent pathological feature was the early (6 hours) raise of calpain-specific alpha II spectrin breakdown products. This is possibly the first reported evidence of spinal cord injury following live exposure of rats to explosive-driven primary blast. While these data need to be verified, in particular excluding a role for artifactual mechanisms mediated by the blast exposure set-up, spinal cord injury should be kept into account in future studies on blast-related neurotrauma.

Keywords: Blast, Traumatic brain injury, Spinal Cord Injury

B7-09

A RAT MODEL OF UNDERBODY BLAST-INDUCED BRAIN INJURY WITH EVIDENCE OF NEUROBEHAVIORAL DEFICITS, NEURONAL DEATH AND INFLAMMATION

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TBI resulting from exposure to explosive-blast targeting military vehicles and their occupants is a major cause of casualties in the recent wars in Iraq and Afghanistan. We developed a rat model of under-vehicle, blast-induced-TBI that at low blast-intensity (50 G force), displays histopathological evidence of diffuse axonal injury and astrocytes activation, but no evidence of neuronal loss and behavioral deficits (Proctor et al., 2014). Here, we assess the impact of increased blast-intensity on neuronal loss, inflammation, behavioral impairments and lethality.

Sprague-Dawley rats (male, 300–350 g), were anesthetized and secured on a platform that was accelerated vertically at 700, 2800 or 4000 Gs after detonation of a small explosive positioned under the platform. Blast and sham animals were subjected to behavioral testing to assess for hippocampus-dependent working-memory and anxiety-like behavior using Y-maze and Plus-maze tests for up to 30 days post-injury, or euthanized at 30 min, 1 or 7 days post-trauma. All animals were euthanized by transcardial perfusion and, brain tissue processed for immunostaining.

We observed a significant increase of cleaved-caspase-3 immunoreactive cells in different brain regions of blast-rats, including the hippocampus, amygdala and cerebellum, starting 30 min post-injury. These cells were mostly neurons. This observation was substantiated by the presence of TUNEL-positive cells in those brain sections and reduced purkinje cells density in the cerebellum. Furthermore, immunostaining for F4/80 showed increased numbers of infiltrated inflammatory cells (macrophage/microglia), predominantly within perivascular and periventricular areas. Animals exposed to 2800G-blast intensity all survived but exhibited significant deficits in hippocampus-dependent working-memory and anxiety-like behavior, as indicated by ANOVA and post-test analysis. Furthermore, 67% of animals subjected to 4000G-blast force died within 4 hours post-blast due to pulmonary hemorrhage.

These findings suggest that our model may be important to further close the gap in understanding the pathophysiology of blast induced-TBI that closely reflects real under-vehicle blast scenarios.

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Keywords: Blast-TBI, Neuronal loss, Inflammation, Neurobehavioral deficits

B7-10

ASSOCIATION BETWEEN APOE GENOTYPE AND NEURODEGENERATIVE PATHOLOGIES AFTER TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) is recognized as a risk factor for neurodegenerative disease; specifically chronic traumatic encephalopathy (CTE). A hallmark pathology of CTE is abnormal accumulation of hyperphosphorylated tau, with many cases also showing pathologies in amyloid-beta. However, these pathologies are not ubiquitous after injury. APOE genotype is recognized to influence acute post-TBI pathology and is also suggested to influence longer-term clinical outcome. This pilot study was designed to investigate the association between APOE genotype and neuropathology after TBI. Cases with a history of single moderate/severe TBI and survival ranging from 28d to 47 years (n = 59) were selected from the Glasgow TBI Archive, together with age-matched controls with no history of TBI (n = 69). Immunohistochemistry for both amyloid and tau was performed and assessed using standardized semi-quantitative grading protocols. APOE genotype was determined using established techniques. Approximately half of TBI and control cases contained amyloid plaques, tau-immunoreactive neurofibrillary tangles or both pathologies. Notably, these pathologies were detected in TBI cases at younger ages and in wider distribution than in non-injured controls, with incidence increasing with age—such that ~90% of TBI cases over age 60 displayed some pathology. Regarding genotype, the APOE-ε4 allele was associated with increased incidence of amyloid pathologies in both control and TBI cases. However, no association was found between APOE genotype and tau pathologies, with or without history of TBI. These preliminary data support previous observations that, for a proportion of patients, TBI survival is associated with the development of more extensive tau and amyloid pathologies when compared to age-matched controls. Further, for the first time, we provide evidence that this late post-TBI pathology may be influenced by genotype, with the development of amyloid pathologies after single moderate/severe TBI apparently influenced by possession of the APOE-ε4 allele.

Keywords: APOE, Amyloid, Tau, CTE, Human

C1 Poster Session V - Group C: Cognition

C1-01

SYMPTOMATIC, PSYCHIATRIC, BEHAVIORAL AND COGNITIVE OUTCOMES IN BLAST EXPOSED VETERANS

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Blast-related mild traumatic brain injury (mTBI) is highly prevalent among OEF/OIF combat veterans. Because many studies employ controls with different baseline characteristics than the blast-exposed subjects, it remains largely unexplored to what extent findings might be attributable to baseline characteristics. We therefore recruited close male relatives to assess outcomes in a cohort of blast-exposed combat veterans. Twenty male OEF/OIF veterans with history of combat blast exposure and 19 matched male close relatives (53% siblings) underwent assessment of multiple TBI outcomes, including PCS, depression, anxiety, stress, PTSD, aggression and cognitive function. Demographics and medical history were compared using unpaired T- and Fisher's exact tests. The outcome measures were assessed with linear regression, adjusting for age, education and employment. False discovery rate (FDR; $\alpha < 0.05$) was used to account multiple comparisons. Z scores were calculated to classify subjects as clinically impaired based on $Z < -1.5$. Veteran and family groups were similar based on demographic, SES, medical history and substance use. Veterans reported worse health related quality of life ($p = 1.7e\text{-}7$), PCS ($p = 1.0e\text{-}6$), and sleep quality ($p = 7.7e\text{-}6$). They exhibited much greater depression ($p = 0.0004$), anxiety ($p = 0.0002$), stress ($p = 0.0001$) and PTSD ($p = 4.0e\text{-}5$) compared to siblings. Veterans also endorsed aggression ($p = 0.013$), and performed worse in measures of attention ($p = 0.007$) and working memory ($p = 0.0003$). All results survived FDR correction. Compared to normative data, veterans had worse symptomatic, psychiatric and cognitive outcomes. Veterans demonstrated excess PCS, psychiatric and cognitive morbidity in the context of an extremely well-matched control sample, which accounts an array of measured (e.g., education, age, race, SES, substance use) and unmeasured (heritability, genetics, social and geographic background) variables. These findings support the relationship of blast to morbidity, suggesting it is not explained by baseline factors, and should inform future studies of combat TBI and TBI in general.

Keywords: Blast, Veterans, Chronic mTBI, Psychosocial outcomes, Family member controls

C1-02

GENDER DIFFERENCES IN EXPOSURE TO AND OUTCOMES OF MILD TRAUMATIC BRAIN INJURY IN AMATEUR ADULT SOCCER PLAYERS

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Female athletes are at increased risk for sports-related mild traumatic brain injury (mTBI) and at increased risk for poor mTBI outcomes, relative to males. Heading in soccer represents a source of repetitive subconcussive head impacts. Previous research has shown that heading exposure above a threshold of approximately 1800 headers/year is associated with deficits in cognitive function including decreased verbal memory performance. This study assesses the role of gender as a predictor of mTBI-associated functional outcomes, including cognitive function and post concussive symptoms (PCS), in a cohort of amateur soccer players. 82 players (41 females and 41 age- and educated-matched males, ages 18–52) were drawn from an ongoing longitudinal study of sub-concussive and concussive mTBI in amateur soccer players. All subjects underwent a battery of cognitive tests and symptoms assessments. Group differences were calculated between men and women using the Mann-Whitney U-test for heading exposure, history of concussion, cognitive performance and PCS at their enrollment visit. Results were corrected for multiple comparisons using false discovery rate (FDR) correction (alpha = 0.05). Men reported more soccer play and more heading during the 12 months prior to enrollment ($p = 0.003$). Women, however, reported more prior concussions ($p = 0.001$), Women also endorsed significantly more acute PCS (headaches, dizziness, and nausea/vomiting) than men ($p = 0.018$). However, men demonstrate decreased performance on a verbal memory task ($p = 0.001$). All reported results survived FDR-correction. These data suggest that women are at increased risk for concussion and PCS, despite lesser overall frequency of soccer play and heading. Men, who report greater exposure to heading, show poorer verbal memory, which is consistent with prior results associating greater heading exposure with deficits in verbal memory.

Keywords: Gender, Sports Related TBI, Concussion, Post Concussive Symptoms

C1-03

MILITARY DEPLOYMENT INCREASES THE RISK FOR TBI FOLLOWING DEPLOYMENT

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The objective of this study was to compare rates of traumatic brain injury (TBI) diagnosis before and after overseas military deployment. We conducted a retrospective examination of a cohort of 119,353 active duty United States military service members (Army, Navy, Air Force, and Marines) whose *first lifetime* overseas deployment began at any time between January 1, 2011 and December 31, 2011 and lasted for at least 30 days. For this cohort, TBI diagnoses were examined during the 76 weeks prior to deployment, during deployment, and for 76 weeks following the end of deployment. The main outcome measure was the rate of TBI diagnosis at sequential 4 week intervals. We found that the risk of being diagnosed with TBI within 4 weeks after returning from deployment was 8.4 times higher than the average risk before deployment. The risk gradually decreased thereafter up to 40 weeks post deployment. During the 41 to 76 weeks following deployment the risk stabilized. The *pre-deployment incidence* of TBI diagnosis was 119.8/100,00 for all services, and was highest for Army (147/100,000). *Following deployment* the incidence of TBI diagnosis was initially as high as 400/100,000 and declined to approximately 200/100,000 at 40 weeks after deployment. At that point the risk ratio for TBI diagnosis stabilized to 1.7 (95% CI: 1.6–1.8) during the 41 to 76 weeks after injury, compared to the pre-deployment risk. These data suggest an increased rate of TBI diagnosis following deployment which, during the first 40 weeks, is most likely a result of a delay in the diagnosis of TBIs that actually occurred while service members were deployed. Both the Department of Defense and the Department of Veterans Affairs have mechanisms for aggressive post-deployment identification of concussions that occured during deployment. However, the stable but increased rate of TBI diagnoses observed at 40–76 weeks following deployment suggests that the *experience of deployment* may increase risk taking behaviors of service members, leading to an increased incidence of TBIs.

Keywords: concussion, Military, deployment, concussion risk, garrison concussion

C1-04

VERY EARLY ADMINISTRATION OF PROGESTERONE DOES NOT IMPROVE COGNITIVE OUTCOMES IN PATIENTS WITH MODERATE TO SEVERE TBI

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Objectives: Despite promising Phase II clinical trial data, early administration of progesterone did not improve gross functional outcomes or mortality in two recent large confirmatory phase III trials of patients with moderate to severe TBI. However, these outcomes may be insufficiently sensitive to treatment effects. This analysis of secondary neuropsychological outcomes evaluates whether progesterone is associated with improved recovery of cognitive functioning.

Methods: A Phase III, double-blind, placebo-controlled trial (ProTECT III) was conducted at 49 Level I trauma centers in the United States. Adults with moderate to severe TBI (GCS score 4 to 12) were randomized to intravenous progesterone or placebo initiated within 4 hours of injury and administered for 96 hours. At 6 months (±30 days), participants capable of testing underwent evaluation of memory, executive functioning, attention, and language.

Results: 546 subjects were testable (263 progesterone, 283 placebo). Analyses of covariance, controlling for potential confounders, did not reveal significant treatment effects for Buschke immediate (41.8 SD-11 progesterone, 42.3 SD-12 placebo) or delayed (5.7 SD-3 progesterone, 5.7 SD-3 placebo) word recall, Trails A sequencing speed (36.5 SD-18 progesterone, 37.0 SD-19 placebo) and Trails B set shifting speed (94.3 SD-54 progesterone, 95.2 SD-57 placebo), digit span forward (9.2 SD-2.1 progesterone, 9.4 SD2.4 placebo) and

backwards (5.7 SD1.9 progesterone, 5.7 SD2.2 placebo), and timed phonemic fluency (31.9 SD-11 progesterone, 29.9 SD-11 placebo). Correlations between neuropsychological and Glasgow Outcome Scale Extended (GOSE) scores were strongest for immediate and delayed recall and sequencing speed.

Conclusion: Consistent with findings using the trial's primary outcome measure (GOSE) in ProTECT III, progesterone did not result in improved cognitive performance 6 months after injury Neuropsychological testing was not shown to be more sensitive to a treatment effect.

Keywords: ProTECT III Clinical Trial, Outcomes, Neuropsychological outcomes, Traumatic Brain Injury, Moderate to severe TBI

C1-05

NEUROANATOMICAL AND COGNITIVE DIFFERENCES IN MILD TRAUMATIC BRAIN INJURY PATIENTS WITH AND WITHOUT POST-TRAUMATIC STRESS DISORDER

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Introduction: Research has revealed increased prevalence of post-traumatic stress disorder (PTSD) following mild traumatic brain injuries (mTBI). While recent studies have focused on characterizing the clinical features of comorbid mTBI and PTSD, few efforts have been made to examine the neuroanatomical sequelae when these conditions occur together. The present analysis seeks to examine volumetric measurements (e.g., frontotemporal cortices and limbic structures) and cognitive functioning in mTBI patients with and without PTSD. We hypothesize that mTBI/PTSD patients will show greater neuroanatomical and cognitive disruptions than mTBI-only patients.

Methods: A total of 23 subjects (78% male) were evaluated between 6–12 months after a mTBI. The subjects completed an MRI and a comprehensive battery of neuropsychological tests assessing attention, learning, memory, executive functions, and processing speed. All participants passed embedded and stand alone measures of effort. Participants were divided into two groups based scores on the PTSD Checklist (PCL). Participants with a PCL score ≥ 44 were included in the PTSD positive group ($n = 11$) while participants with score ≤ 20 were included in the PTSD negative group ($n = 22$). Volumetric analysis was performed using T1-weighted MPRAGE scans acquired on a Siemens Biograph MR 3T. Images were segmented using the longitudinal pipeline within the FreeSurfer software package (Version 5.3).

Results: Our analyses showed patients with mTBI/PTSD exhibited greater reductions in brain volumes and poorer performance on neuropsychological tests relative to mTBI-only patients. Specifically, mTBI/PTSD patients showed localized reductions in the middle frontal ($F = 12.9$, $p = .001$), middle temporal ($F = 7.15$, $p = .012$) and parahippocampal gyri ($F = 4.38$, $p = .045$). Additionally, impairments in processing speed (Trails Making Test A, Symbol Search, Coding; p's $< .01$) and memory encoding (California Verbal Learning Test, $p = .022$) were evident in the mTBI/PTSD group.

Conclusions: Individuals with combined mTBI/PTSD have abnormalities beyond those evident in mTBI alone. These changes include impairments in processing speed, memory, and anatomic changes in regions resembling the default mode network (Lanius et al., 2010).

Keywords: Post Traumatic Stress Disorder, Neuropsychological, Brain Volume, Comorbid disorders

C1-06

THE EFFECT OF SINGLE VS. MULTIPLE HEAD INJURIES ON BEHAVIORAL AND COGNITIVE OUTCOMES

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Traumatic brain injury (TBI) can result in functional impairment and neuropathological changes. Research suggests that repetitive injury may result in chronic traumatic encephalopathy (CTE). However, the relationship of repetitive TBI and subconcussive blows in the neurodegenerative process is unclear. This study analyzed behavioral and cognitive outcomes in patients reporting single versus multiple traumatic brain injuries, and also examined the effect of reported subconcussive blows. The subjects were enrolled in a longitudinal study and were seen at baseline (30, 90, or 180 days after brain injury) and followed up at one year. The Ohio State University TBI Identification Method was used to determine number and severity of TBIs. The outcomes assessed at one year included: Neurobehavioral Symptom Inventory (NBSI), Beck Depression Inventory (BDI), Booklet Category Test (BCT), Brief Symptom Inventory (BSI-18), Finger Tapping Test, and Wechsler Adult Intelligence Scale 4th Edition (WAIS-IV). Thirty-six patients were enrolled in the study (64% male, average age 44.0 years). Twenty eight percent of the patients had mild injuries, 56% had moderate, and 17% had severe injuries. Sixty one percent had a single injury, while 39% had two or more TBIs. Fifty percent of patients reported no subconcussive blows, 33% reported one or two subconcussive blows, and 17% reported three or more. Those with multiple head injuries had 7-point higher NBSI, 6-point higher BDI, and 6-point higher BSI scores compared to those with single head injuries ($p = 0.02$, $p = .003$, and $p < .0001$, respectively) after controlled for age, severity, and sex. There were no significant differences in cognitive outcomes for single versus multiple injuries or subconcussive blows in working memory, processing speed, or motor functioning. Our results suggest that individuals with a history of multiple TBIs are at risk for worsened behavioral outcomes compared to those with a single injury. However, repetitive injury (including subconcussive blows) did not appear to affect cognitive outcomes at 1 year.

Keywords: Behavioral Outcomes, Multiple Head Injuries, TBI, Subconcussive blows

C1-07

MICE, TRAUMATIC BRAIN INJURY, AND COGNITIVE EFFECTS OF ENRICHED ENVIRONMENT

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To date, there is yet no established effective treatment (medication or cognitive intervention) for post-traumatic brain injury (TBI) patients with chronic sequelae. Enriched Environment (EE) has been recognized of importance in brain regulation, behaviour and physiology. Rodents reared in, or pre-exposed to EE, recovered better from brain insults. Using the concussive head trauma model of minimal TBI in mice, we evaluated the effect of transition to EE following a weight-drop (30 gr or 50 gr) induced mTBI on behavioural and cognitive parameters in mice in the Novel Object Recognition task, the Y- and the Elevated Plus mazes. In all assays, both mTBI groups (30 gr, 50 gr) housed in normal

conditions were equally and significantly impaired 6 weeks post injury in comparison with the no-mTBI ($p < 0.001$ and $p < 0.03$ respectively) and the mTBI + EE groups ($p < 0.001$ for the 30 g, and $p < 0.017$ for the 50 g). No differences were found between the control and the EE mice. Two separate finding emerge: (1) the significantly positive effects of the placement in EE following mTBI, on the rehabilitative process of the tested behaviors in the affected mice; (2) the lack of difference between the groups of mice affected by 30 gr or by 50 gr. Further studies are needed in order to characterize the exact pathways involved in the positive effects of the EE on mice recovery from mTBI. Possible clinical implications indicate the importance of adapting correlates of EE to humans, i.e., prolonged and intensive physical activity – possibly combined with juggling training and intensive cognitive stimulation.

Keywords: Enriched Environment, Novel Object Recognition, Y maze, mice

C1-08

TRAUMATIC BRAIN INJURY CORRELATES IN A VULNERABLY HOUSED POPULATION

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Background: Marginally housed or homeless populations have elevated rates of medical and psychiatric illness, and may have a higher rate of traumatic brain injury (TBI). TBI may act to predispose, trigger, or perpetuate many other adverse health issues.

Objective: To describe the frequency and severity of TBI in a sample of marginally house individuals resident in Vancouver's downtown single room occupancy (SRO) hotels, and to characterize the relationship between TBI and multiple health parameters in this population.

Methods: A prospective community sample of 297 individuals was evaluated at baseline with psychiatric and neurological assessments, cognitive testing and multimodal MRI.

Results: 185 of 297 subjects (62%) endorsed a previous history of any serious face of head injury. 37% (108) of subjects endorsed TBI as defined by loss of consciousness or confusion after the head trauma, and 81.7% of these were males. Assault was the most common mechanism (41%) followed by falls (14%). The distribution of mild, moderate, and severe TBI was 33%, 27%, and 19% respectively, and we were unable to accurately determine severity in 21%. Magnetic Resonance Imaging showed significant encephalomalacia consistent with head trauma in 15 subjects (5% of the total sample). Compared to subject with no history of TBI, those with TBI reported more dizziness and fainting ($p = 0.001$), seizures ($p = 0.031$), and memory complaints ($p = 0.02$). In addition, subjects with TBI were more likely to have a history of alcohol dependence ($p = 0.012$), a diagnosis of bipolar I disorder ($p = 0.047$) and to have been charged with a criminal offense ($p = 0.014$). There were no differences on neuropsychological testing between the groups.

Conclusions: Individuals in marginalized housing have a high rate of TBI and trauma related findings on cranial MRI. Neuropsychiatric correlations of TBI in this group include dizziness, fainting, memory problems, seizures, alcohol dependence, bipolar disorder and criminality. These findings suggest that specialized acquired brain injury services may benefit vulnerably housed individuals.

Keywords: Traumatic Brain Injury, homeless, marginalized housing, Psychiatry

C1-09

CONTROLLED CORTICAL IMPACT INCREASES COCAINE INTAKE IN RATS: A POTENTIAL ROLE FOR NEUROINFLAMMATION IN ADDICTION

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Recent clinical evidence has begun to show relationships between traumatic brain injury (TBI) and numerous psychiatric disorders. One large concern put forth by clinicians is the possibility that TBI and drug addiction may be linked. However, it is difficult to elucidate causation of this relationship in clinical settings due to the complex history of individuals. In the current study, we combined a well-established rat model of TBI and addiction in order to determine if brain injury increased risk for addiction. Rats were given a bilateral controlled cortical impact over the frontal cortex at either severe (3 m/s, 2.5 mm depth) or milder (1 m/s, 0.8 mm depth) settings or a sham procedure. After one week, rats underwent a second surgery to implant a catheter into the jugular vein. A week later, they were placed in operant chambers to self-administer IV infusions of cocaine (0.5 mg/kg/infusion) or saline for 6 hours/day over a 10 day period. Rats were euthanized at day 25 post-injury and cortical samples collected to measure inflammatory markers via multiplex ELISA. All cocaine-treated rats pressed the lever more and received more infusions than saline rats regardless of injury. Brain-injured rats (both severe and mild) pressed more for cocaine and received more infusions than sham rats. Severe-injured rats were slower to discriminate the active lever from the inactive lever. Levels of multiple inflammatory cytokines were increased as a result of cocaine intake and TBI. A principal components analysis revealed general patterns of change as a result of cocaine self-administration and TBI with cocaine intake increasing inflammatory cytokines in sham animals, but decreasing these markers in injured animals. These novel data demonstrate a causal link between TBI and addiction and suggests that proinflammatory cytokines may be responsible for this effect. Increases in neuroinflammation following brain injury may resemble processes found in cocaine addiction that predispose individuals to the addictive effects of drugs.

Keywords: Addiction, Cytokine, Controlled cortical impact, Cocaine, Self-Administration

C1-10

STIMULUS-SPECIFIC ENHANCED CONTEXTUAL FEAR LEARNING FOLLOWING LATERAL FLUID PERCUSSION EXPERIMENTAL TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) is a silent epidemic and is labeled the signature injury of troops in OIF/OEF combat operations, a population that are often exposed to stressful stimuli and emotional trauma. While TBI is typically known to impair learning and memory for neutral events, traumatic fear memories are enhanced after TBI, consistent with increased prevalence of comorbid TBI and post-traumatic stress disorder (PTSD). Changes in sensitivity to sensory

stimuli are common after TBI, and might influence the encoding of traumatic events. Our lab has shown enhanced contextual fear after lateral fluid percussion injury (LFPI) when fear conditioned after injury with white noise cues paired with footshocks (Reger et al., *Biol. Psychiatry*, 2012). In the current study we show that compared to sham, LFPI did not impact acquisition, context, or cued fear when conditioned with low frequency (2800 Hz), pure tones. Given that white noise encompasses a greater frequency range, we hypothesize that LFPI enhances contextual fear to white noise-signaled conditioning due to injury-induced altered sensory processing. In a second experiment, LFPI or sham rats were pre-exposed to white noise trials, then were fear conditioned and tested for contextual and cued fear on subsequent days. Interestingly, LFPI rats showed elevated freezing to the white noise (16.8% vs. 4.2%, $p < 0.001$) and context (32.6% vs. 7.1%, $p < 0.001$) during the pre-exposure session, and during baseline the next day (6.9% vs. 1.2%, $p = 0.035$), suggesting that LFPI rats conditioned to white noise alone. Furthermore, LFPI rats displayed enhanced contextual fear in the days after conditioning (day 1 freezing: 83.1% vs. 56.6%, $p = 0.001$). These data provide implications for altered sensory processing after TBI, where otherwise neutral stimuli may adopt aversive properties and impact encoding of traumatic memories.

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Keywords: sensory, fear conditioning, post traumatic stress disorder, amygdala

C1-11

APOE-ε4 IS ASSOCIATED WITH DECREASED SIX-MONTH VERBAL MEMORY PERFORMANCE AFTER MILD TRAUMATIC BRAIN INJURY

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Mild traumatic brain injury (MTBI) is a cause of cognitive impairment, which may be modulated in part by genetic susceptibility. Apolipoprotein E (*APOE)* encodes a lipoprotein released after brain injury with neurotropic effects. Of its three isoforms (*ε2/ε3/ε4*), presence of the *ε4* allele (*APOE-ε4)* is known to associate with impaired memory in neurodegenerative diseases. However, its association with memory function after MTBI remains unclear. We utilized the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) Pilot study to investigate whether *APOE-ε4* influences six-month verbal memory, measured by four subscales of the California Verbal Learning Test (CVLT): Short-Delay Free Recall (SDFR), Short-Delay Cued Recall (SDCR), Long-Delay Free Recall (LDFR) and Long-Delay Cued Recall (LDCR). Results in 114 adult MTBI patients with no surgical intervention demonstrate that *APOE-ε4* significantly associates with long-term memory (LDFR: mean decrease 1.19 points, 95% CI [−2.31, −0.01], $p = 0.048$; LDCR: −1.57, [−2.60, −0.54], $p = 0.003$) after controlling for effects of age, race, years of education, and presence of intracranial pathology on CT. The association between *APOE-ε4* and short-term memory showed significance in SDCR (-1.04, [-2.06, −0.01], $p = 0.047$) and a statistical trend in SDFR (-1.08, [-2.34, 0.17], $p = 0.090$) after controlling for age, race, education and CT. These results support the need for additional research to confirm and extend these findings. *APOE-ε4* may confer an increased risk for verbal memory disturbances in patients with MTBI, with implications for prognosis following MTBI.

Keywords: Clinical Trial, Human Studies, Mild TBI, Outcome

C1-12

POSITIVE ALLOSTERIC MODULATION OF THE α7 NICOTINIC ACETYLCHOLINE RECEPTOR REVERSES CHRONIC COGNITIVE DEFICITS AFTER TBI

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Traumatic brain injury (TBI) causes profound changes within the hippocampus that chronically hinder cognitive recovery. Both clinical and preclinical studies have established that cholinergic signaling is decreased following TBI. This decreased signaling is reminiscent of Alzheimer's disease, where cholinesterase inhibitors are successful, major clinical therapeutics. Clinical trials for TBI have had only modest success using cholinesterase inhibitors, and are limited by only broadly and nonspecifically raising acetylcholine levels. As an alternative therapeutic strategy, we hypothesize that targeting the α7 nicotinic acetylcholine receptor (nAChR) with a positive allosteric modulator will promote cognitive functioning in the chronic recovery period of TBI, by potentiating cholinergic signaling only when endogenous ligand is bound to the receptor. To test this hypothesis, adult male Sprague Dawley rats received moderate parasagittal fluid-percussion brain injury or sham surgery. At 3 months after recovery, animals were treated with vehicle (2% DMSO, 8% solutol, 90% saline), or AVL-3288 (0.3 mg/kg, i.p) 30 min prior to behavioral training. Animals were trained on fear conditioning and the water maze. TBI-induced learning and memory deficits in cue and contextual fear conditioning and the water maze were significantly reversed with AVL-3288 treatment. We further assessed the effects of AVL-3288 on the expression of long-term potentiation (LTP) in area CA1 of the hippocampus. Our preliminary data from hippocampal slices at 3 months after TBI or sham surgery revealed that expression of LTP was significantly decreased after TBI as compared to sham animals. AVL-3288 treatment (1 μM) during LTP induction reversed the TBI-induced deficits in LTP. These results indicate that AVL-3288 improves learning and memory performance after TBI in the chronic recovery period. These findings support the feasibility of using positive allosteric modulators of the α7 nAChR for the treatment of cognitive deficits after TBI.

Keywords: Traumatic Brain Injury, α7 nicotinic acetylcholine receptor, Long-term potentiation, Learning and memory

C1-13

DOSE-RESPONSE EVALUATION OF KOLLIDON IN THE MIAMI FLUID PERCUSSION MODEL OF TRAUMATIC BRAIN INJURY: AN OBTT CONSORTIUM STUDY

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Kollidon (VA64) is a compound with several potential mechanisms useful in treating traumatic brain injury (TBI). Published reports have shown that VA64 reseals membranes, reduces blood brain barrier breakdown and necrosis as well as reducing motor deficits. Male Sprague-Dawley rats were anesthetized and underwent moderate fluid percussion (FP; 1.8–2.1 atm) TBI or sham surgery. Rats were randomized into three treatment groups and administered VA64 (0.2 g or 0.4 g/5 ml IV) or vehicle. Animal groups were TBI-VA64-Low (n = 15), TBI-VA64-High (n = 15), TBI-Veh (n = 15) or Sham (n = 15). Rats were tested on day 7 post-injury for sensorimotor function (gridwalk, cylinder task). On days 13–21, rats were assessed for cognitive function utilizing the simple place task, probe trial and working memory task. On day 21, brain tissue was processed for histology. One-way ANOVA was not significant for the cylinder task ($p < 0.05$) but was for the left forelimb of the gridwalk task ($p < 0.05$). Both dosages worsened outcome on this task compared to TBI-Veh. For the hidden platform task, two-way repeated measures ANOVA for latency was significant for group ($p < 0.05$) but not for group x day. However, neither dosage improved function on this task compared to TBI-Veh. There was no significant difference between groups for the probe trial. Repeated measures ANOVA for working memory latency was significant for trial ($p < 0.001$), but not group or group x trial. Histopathological analysis is currently being assessed. We conclude that treatment with either dosage of VA64 after FP did not improve sensorimotor or cognitive function. In fact, left forelimb footfaults were increased with this drug. At this time, although histology and biomarker data are still pending, behavioral findings of VA64 treatment in the FPI model in rats do not support its further testing in OBTT. Support: US Army W81XWH-10-1-0623.

Keywords: Kollidon, OBTT, fluid percussion

C1-14

PERSISTENT BEHAVIORAL DEFICITS IN RATS AFTER MODERATE FLUID-PERCUSSION INJURY

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Background: Although traumatic brain injury (TBI) is beginning to be viewed as a chronic disease, few rodent studies have investigated the long-term behavioral deficits elicited by well-established rodent models of injury. The data presented here are an initial demonstration of which behavioral measures, commonly used in TBI research, provide useful indications of long-term effects of brain injury in rodents.

Methods: Male Sprague-Dawley rats (250–300 g) were acclimatized to handling and pre-trained to vestibulomotor tasks and neurological testing prior to receiving moderate fluid-percussion-injury (FPI) or sham-injury under general anesthesia. Rats were subjected to simple reflex tests (Neuroscore) as well as beam-balance and beam-walking tasks for 3 days immediately post injury. Rats were kept pair-housed, handled and weighed twice weekly and then retested either 3 or 6 months after injury on the same tasks followed by a working memory version of the Morris water maze.

Results: On post-injury days 1 – 3, Two-factor ANOVA revealed significant effects of injury on Neuroscore, Beam-Balance, and Beam-Walk ($P < 0.001$), a significant effect of time ($P < 0.001$), and a significant interaction ($P < 0.001$). At 3 and 6 months post-injury, there were no significant differences between injured and sham rats in the Beam-Balance or Beam-Walk tasks. However, a significant effect of injury on Neuroscore persisted at both 3 ($P < 0.01$) and 6 months ($P < 0.05$) as well as on the working memory test at 3 ($P < 0.001$) and 6 ($P < 0.001$) months post injury.

Conclusions: These data suggest that vestibulomotor and coordination function recover within 3 months of a moderate injury, while neurological and cognitive deficits persist out to 6 months after injury. Therefore reflex testing and working memory water maze are useful measures of behavioral deficits that persist after injury.

Support: These studies were completed as part of an interdisciplinary research team funded by The Moody Project for Translational Traumatic Brain Injury Research.

Keywords: Traumatic Brain Injury, Behavior, Morris Water Maze, behavioral assessments

C2 Poster Session V - Group C: Gene Expression

C2-01

MENINGEAL INJURY DETECTED BY CONTRAST ENHANCED FLUID-ATTENUATED INVERSION RECOVERY IMAGES AND DIFFERENTIAL GENE EXPRESSION

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Injury to the meninges is concomitant with TBI. In subjects who sustained a meningeal injury, the highly sensitive fluid-attenuated inversion recovery (FLAIR) MRI following gadolinium contrast administration reveals enhancement of the meninges, an image that standard scans cannot capture. The pathogenesis of this so called traumatic meningeal injury (TMI) is not yet understood. By comparing gene expression data from head injured subjects with isolated TMI, to similar subjects that are imaging negative, we hope to identify pathways specific to meningeal injury and resulting secondary damage. All subjects received a standard research MRI, contrast enhanced FLAIR scan, and blood sample collection within 48 hours of injury. Two groups of subjects were included, those; i) without any imaging abnormalities (TMI-) and ii) with enhancement of the meninges on post contrast FLAIR (TMI+) but with no other imaging abnormality. Groups were compared on microarray gene expression using peripheral samples of blood. Extracted RNA was analyzed using GeneChip 3′ IVT Expression kit and Affymetrix. Partek Genomics Suite software was used to compare gene expression. Forty subjects were included, 23 participants in the TMI- group, and 17 participants in the TMI + group. Loss of consciousness occurred in 27 participants, and 25 had posttraumatic amnesia. TMI was seen most frequently in the falx (n = 15). We observed 77 genes that were differentially expressed in the TMI + group compared to the TMI- group, of which have been previously associated with initiating inflammatory mediators,

phagocytosis, TBI, and other regulatory mechanisms. In addition, a dichotomized categorization when inputting the differentially expressed genes revealed over half of the patients could be correctly clustered in their respective TMI + and TMI- groups. These findings suggest that TMI may be a distinct, highly prevalent, phenotype that is relevant to the pathogenesis of acute TBI.

Keywords: imaging, meningeal, biomarkers, gene-expression

C2-02

A COMPARATIVE STUDY ON SERUM MICRORNA BIOMARKER SIGNATURES OF MILD TRAUMATIC BRAIN INJURY AND POSTTRAUMATIC STRESS DISORDER

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Mild traumatic brain injury (mTBI) is often associated with post-traumatic stress disorder (PTSD) in combat scenario as well as in certain civilian cases. However, it is difficult to distinguish mTBI and PTSD due to overlapping symptoms between them. The emerging evidences of PTSD prevalence in combat soldiers suggest the importance of developing sensitive and specific diagnostic markers for PTSD and mTBI. MicroRNAs (miRNAs) are small, endogenous, evolutionarily conserved noncoding RNA and the key regulators of gene expression. Recently, circulating miRNAs in blood have been reported to be sensitive and specific biomarkers of various diseases and disorders including brain injury. In this study, we used a mouse model of weight drop injury to recreate closed head TBI and a rat learned helplessness stress model for PTSD. Serum was collected at 3 h following four different closed head injury (CH-TBI) groups and 3h and day 14 of PTSD. MiRNA profiling in serum showed thirteen and nine common miRNAs among four CH-TBI groups and PTSD serum and amygdala, respectively. However, the comparison of altered serum miRNAs of CHI-TBI and PTSD showed no correlation. Pathway analysis of thirteen miRNAs and their validated targets showed few of them to have a direct correlation with axon guidance, depression and sensorimotor impairment associated pathways. Comparison of altered serum miRNAs between CH-TBI and PTSD showed no correlation. The difference in the serum miRNA expression signature could be an outcome of the different functional pathways activated post TBI or stress exposure in the brain which in turn gets reflected in the alteration of the global serum miRNA profile. These results suggest that miRNA signatures can be used for the differential diagnosis of PTSD and TBI.

Acknowledgments

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Keywords: miRNA, serum biomarker, TBI, PTSD, Differential diagnosis

C2-03

TRANSCRIPTOMICS OF AGGRAVATED EPILEPTOGENESIS AND COGNITIVE DECLINE AFTER TBI IN APP/PS1 MOUSE MODEL OF ALZHEIMER'S DISEASE

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Objectives: To test the hypothesis that amyloidogenic genetic background predisposes to worsening of post-TBI outcome, we investigated whether TBI in the APP/PS1 PS1 mouse model of AD aggravates epileptogenesis, enhances somatomotor and cognitive impairment, and associates with long-term changes in the expression of genes involved in the amyloidogenic and Tau pathways.

Methods And Results: Mild (mTBI) or severe TBI (sTBI) was triggered using controlled cortical impact (CCI) in APP/PS1 mice and wild-type (wt) littermates. Composite neuroscore showed that the TBI severity but not APP/PS1 genotype had an effect on somatomotor performance during the first 2 wk post-TBI ($p < 0.001$). Morris water-maze (MWM) revealed a genotype effect on TBI-induced impairment in spatial learning and memory as APP/PS1-sTBI mice performed more poorly than Wt-sTBI mice ($p < 0.05$). Both TBI severity and genotype affected epileptogenesis, as 88% of APP/PS1-sTBI mice had epilepsy which was greater than that in the Wt-sTBI (11%, $p < 0.01$) or APP/PS1-sham group (50%, $p < 0.05$). Gene expression profiling of the perilesional cortex, ipsilateral thalamus, and ipsilateral hippocampus was performed at 16 wk post-TBI using an Affymetrix microarray system. Of the 133 genes involved in the amyloidogenic and Tau pathways, sTBI induced transcriptional changes in 17 genes in Wt mice and in 10 genes in APP/PS1 mice. The seizure frequency correlated with the cortical expression of Nos1 ($r = 0.83$) and Mapk3 ($r = 0.67$). Immunohistochemical analysis confirmed increased expression of Nos1 protein in neuronal somata and processes in the perilesional cortex of APP/PS1 mice as compared to APP/PS1-sham ($p < 0.05$) or Wt-sTBI groups ($p < 0.01$). Motor impairment correlated with the cortical expression of genes encoding amyloid clearing proteins, such as Clu ($r = 0.83$), Abca1 ($r = 0.78$), A2m ($r = 0.76$), Apoe ($r = 0.70$), and Ctsd ($r = 0.63$).

Conclusions: The present study provides the first comprehensive evidence of the causal role of the AD genotype in the exacerbation epileptogenesis after TBI.

Keywords: Alzheimer's disease, epileptogenesis, post-traumatic epilepsy, bioinformatics

C2-04

AEROMEDICAL EVACUATION-RELEVANT HYPOBARIA WORSENS TBI IN RATS EXPOSED TO UNDERBODY BLAST-INDUCED HYPERACCELERATION

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Occupants of vehicles targeted by IEDs are often victims of TBI and are typically air-evacuated (AE) to a regional medical center within a few days post-injury. This study tested the hypothesis that exposure of rats to AE-relevant hypobaria worsens damage to white matter and blood vessels caused by blast-induced acceleration. The underbody blast paradigm (Proctor et al., 2012) resulted in peak vertical acceleration of adult male rats equal to 100 Gs without exposure to blast overpressure. Rats remained under normobaric conditions or were exposed

to hypobaria equal to 8000 ft for 6 hr, starting at 6, 24, 72 hr or 6 days post-blast. At 7 days post-blast, rats were perfusion-fixed and their brains analyzed for evidence of axonal fiber injury and cerebrovascular injury. Other rats were used for neurobehavioral assays at 14 days. The number of de Olmos silver-stained axonal fibers present in the internal capsule was two-times greater in animals (10/group) exposed to 100 G blast than in shams. Animals exposed to 6 hr hypobaria at 6, 24, 72 hr and 6 days after blast all exhibited significantly more silver-stained fibers than those not exposed to hypobaria. Rats exposed to 100% O_2 during hypobaria at 24 hr post-blast displayed significantly greater silver staining than those exposed to 21% O_2 (room air) during hypobaria. The cortical area occupied by von Willebrand Factor (vWF) immunoreactivity was very low in shams and over ten-times greater in blast/normobaric animals or blast/hypobaric animals. Quantitative rtPCR indicated a 10-fold increase in vWF gene expression at 7 days post-blast. The number of foot-faults observed during the balance beam test was significantly greater in blast/hypobaric (100% O_2) animals compared to shams, or blast/hypobaric (21% O_2) animals. We conclude that AE-relevant hypobaria worsens brain injury in rats cause by blast-induced acceleration and that this injury is further exacerbated by exposure to 100% O_2 during hypobaria. Supported by US Air Force FA8650-11-2-6D04 and US Dept. of Defense W81-xWH-13-1-0016

Keywords: blast, axonopathy, hypobaria, vasculopathy

C2-05

DIFFUSE TRAUMATIC BRAIN INJURY RESULTS IN BIMODAL VARIATION OF SYNAPTIC MARKER EXPRESSION IN THE SOMATOSENSORY CORTEX OVER TIME

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Diffuse traumatic brain injury (dTBI) induces multifocal axonal pathology and deafferentation, which subsequently leads to axonal regeneration. Over time this regeneration may result in adaptive and maladaptive circuit reorganization, with synaptogenesis being integral to the reorganization process. The time course for synaptogenesis is not well understood. In rodents, dTBI results in late-onset sensory-sensitivity (neurological impairment) to whisker stimulation, with evidence of maladaptive circuit reorganization in the thalamocortical circuit. We test the hypothesis that dTBI results in a burst of synaptogenic marker expression in the somatosensory cortex (S1BF), which would define the time-frame of circuit reorganization. Adult male Sprague-Dawley rats underwent sham or moderate midline fluid percussion injury. At nine time points over 2 months post-injury, biopsies from the S1BF were processed for gene and protein expression of synaptogenic markers using qPCR and automated capillary westerns. Initial studies have revealed a significant change in gene expression of both pre-synaptic (synaptophysin; SYN) and post-synaptic (post-synaptic density protein of 95 kDa; PSD-95) markers in the S1BF. Both SYN and PSD-95 show bimodal variations in gene expression over time; $F(9,48) = 3.923$; $p = 0.0009$ and $F(9,49) = 4.184$; $p = 0.0005$, respectively. Protein quantification of SYN and PSD-95 in the S1BF are ongoing. These studies will provide a better understanding of the temporal profile of synaptogenic events after dTBI in the S1BF. This knowledge will lend insight to the anatomical mechanisms by which circuit reorganization leads to late-onset sensory sensitivity to whisker stimulation. Therapies to regulate injury-induced synaptogenesis may mitigate neurological impairment.

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Keywords: Traumatic brain injury, Synaptogenesis, Circuit reorganization, Primary somatosensory cortex

C2-06

DRD2 C957T POLYMORPHISM IS ASSOCIATED WITH IMPROVED 6-MONTH VERBAL LEARNING FOLLOWING TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) often results in variable clinical outcomes, which may be influenced by genetic variation. A single-nucleotide polymorphism in the dopaminergic receptor type d2 (*DRD2)* may influence cognitive deficits following TBI. However, associations with *DRD2* were more recently attributed to genetic variability within the adjacent ankyrin repeat and kinase domain containing 1 protein (*ANKK1*). Here, we utilize the Transforming Research and Clinical Knowledge in Traumatic Brain Injury Pilot (TRACK-TBI Pilot) study to investigate whether a novel *DRD2* C957T polymorphism (rs6277) influences outcome on a cognitive battery 6-months following TBI – California Verbal Learning Test (CVLT), Wechsler Adult Intelligence Test Processing Speed Index Composite Score (WAIS-PSI), and Trail Making Test (TMT). Results in 128 Caucasian subjects show that rs6277 T-carriers associates with better verbal learning and recall on CVLT Trials 1–5 (mean increase 5.0; 95% CI [0.8 to 9.2], $p = 0.02$), Short-Delay Free Recall (mean increase 1.3, 95% CI [0.1 to 2.6], $p = 0.04$), and Long-Delay Free Recall (mean increase 1.3, 95% CI [0.1 to 2.6], $p = 0.04$), which persist after controlling for age, education years, Glasgow coma scale on admission and, most notably, genotype of at least one common SNP within *ANKK1* (rs1800497). No association was found between the rs6277 polymorphism and processing speed (mean increase 1.43 seconds; 95% CI [-4.1 to 7.0], $p = 0.61$) or mental flexibility (mean decrease 16.1 points; 95% CI [-34.3 to 2.2], $p = 0.08$) on WAIS-PSI and TMT, respectively. Hence, the *DRD2* polymorphism rs6277 may be associated with better performance on select cognitive domains independent of *ANKK1* following TBI.

Keywords: TBI, outcomes, DRD2, CVLT

C2-07

BRAIN HYPOXIA RESPONSIVE GENE EXPRESSION IN SEVERE TRAUMATIC BRAIN INJURY PATIENTS

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Objective: Brain tissue oxygenation ($PbtO_2$) monitoring has been utilized in the severe traumatic brain injury (sTBI) population as an *in vivo* tool to detect oxygenation changes in the acute recovery phase. It has been previously reported that the longer the time a patient experiences a $PbtO_2$ of ≤15 torr, the greater the likelihood of death. The purpose of this study is to assess $PbtO_2$ values and its relationship to hypoxia responsive gene expression.

Methods: Age, gender and initial Glasgow Coma Scale (GCS) score matched cohorts ($PbtO_2 < 15$ mmHg and $PbtO_2 \geq 30$ mmHg) of severe TBI patients (n = 20) were assessed. Post-trauma day 1 blood samples were collected via Paxgene tubes and processed for gene expression utilizing the Ilumina Human HT12 expression BeadChip technology. For the comparison of low $PbtO_2$ vs high $PbtO_2$, differentially expressed genes were identified using data analysis methods selected by efficiency analysis (EA) using Auto AE software. Raw expression values were normalized through the Gene Expression Data Analysis (GEDA) tool and the J5 test was used at a threshold of 33 to identify differently expressed genes.

Results: Post-trauma day 1 gene expression was significantly higher in the low $PbtO_2$ cohort for neonatal hemoglobin, gamma G (HBG2) and gamma A (HGB1), and ferritin (J5 values 164.1, 128.3 and 45.5 respectively) and also hypoxia-responsive genes associated with hypoxia inducible factor (HIF-1α), S100A4 and annexin A1(J5 values 45.3 and 14.72, respectively).

Conclusion: Increased gene expression for higher-affinity fetal hemoglobin, increased iron storage and hypoxia-responsive genes occurred in a low brain oxygenation state following TBI. With additional study, these pathways may represent a therapeutic avenue to treat brain hypoxia in the injured brain.

Keywords: traumatic brain injury, hypoxia, brain tissue oxygenation, fetal hemoglobin

C2-08

GENOME-WIDE CHANGES IN GENE EXPRESSION FOLLOWING SPORTS-RELATED CONCUSSION

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Objective: To determine changes in global gene expression (GE) following sport-related concussion (SRC).

Methods: From 2010–2012, 253 NCAA collegiate contact athletes from two universities in Rochester, New York, underwent collection of peripheral blood mononuclear cells (PBMC) at the start of the sport season (baseline). Sixteen athletes who subsequently developed a SRC, along with 16 non-concussed teammates who served as controls, underwent repeat collection of PBMC within 6 hours of injury (acutely). Concussed athletes underwent additional PBMC collection at 7 days post-injury (sub-acutely). PBMC mRNA expression at baseline was compared to mRNA expression acutely and sub-acutely post-SRC. Ingenuity Pathway Analysis was used to translate differential GE into gene networks most likely affected by SRC. Clinical recovery was determined by examining changes in post-concussive symptoms, postural stability, and cognition from baseline to the sub-acute timepoint.

Results: Athletes with SRC had significant changes in mRNA expression at both the acute and sub-acute timepoints compared to their baseline profiles. There were no significant GE changes among uninjured teammate control athletes. Acute transcriptional changes centered on inflammatory activity with key transcriptional hubs being interleukins 6 and 12, toll-like receptor 4, and NF-κB. Sub-acute GE changes centered on glucocorticoid receptor signaling with NF-κB, follicle stimulating hormone, chorionic gonadotropin, and protein kinase catalytic subunit being the key transcriptional hubs. All concussed athletes were recovered by the sub-acute timepoint.

Conclusion: Acute post-SRC gene transcriptional changes reflect regulation of the innate immune response as well as the transition to an acquired, adaptive immune response. By 7 days post-injury, transcriptional activity is centered on the regulation of the hypothalamic-pituitary-adrenal axis. These findings illustrate a time-dependent shift in GE post-injury that may provide insight into the pathophysiology of recovery from SRC and suggest putative targets for therapeutic intervention.

Keywords: gene expression, concussion, sports, clinical research

C2-09

PATHWAY ANALYSIS OF LONG TERM GENOMIC CHANGES AFTER EXPERIMENTAL TBI

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Background: Despite expansive literature on the acute effects of traumatic brain injury (TBI), much less is known about the causal injury mechanisms that trigger chronic neurodegenerative changes. Here, we examined genomic changes that persist from 24 hours up to 3 months after TBI, and test our hypothesis that a core set of dysregulated genes/pathways could be associated with long-term neurodegeneration.

Methods: Male, Sprague-Dawley rats (300–350 g) were anesthetized (isoflurane), subjected to moderate fluid percussion TBI, and survived 24 hr or 3 months. Sham animals received the same anesthetic regimen, surgical preparation, and survival time points, but no injury. Hippocampal regions were microdissected and sent to GenUs BioSystems for genome-wide microarray analysis (Agilent Rat GE 8x60K arrays). Quantitative real-time PCR, using individual Taqman assays, was performed to validate selected gene expression changes in pathways activated/inhibited by TBI.

Results: 24 h post-injury, 554 genes ($p \leq 0.05$, fold-change ≥ 1.5) on the microarray were differentially expressed, compared to sham injured control samples. At 3 months, 83 genes ($p \leq 0.05$, fold-change ≥ 1.5) were differentially expressed. Using gene expression analysis tools in Ingenuity Pathway Analysis software, we constructed causal and network interactions among the differentially expressed genes, which allowed us to infer the effects of TBI on critical cell signaling pathways. Genes commonly found dysregulated after TBI acutely (24 h) and chronically (3 months) are members of cell signaling pathways that are critical for cell survival/death (PI3K signaling), neurodegeneration (RHOGDI), inflammation (acute phase response), and immune response (complement system activation).

Conclusion: These data support our hypothesis that chronic neurodegeneration may be linked to the persistent (up to 3 month) expression of critical hub genes that are important for cell survival/death. Understanding the molecular mechanisms underlying chronic neurodegenerative processes will enable the development of targeted therapies for TBI and aid in characterizing biomarkers for diagnosis.

Support: These studies were completed as part of an interdisciplinary research team funded by The Moody Project for Translational Traumatic Brain Injury

Keyword: Chronic

C2-10

PATHWAY ANALYSIS OF NEUROPROTECTIVE DRUG TREATMENT AFTER ACUTE TRAUMATIC BRAIN INJURY

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Background: The current lack of therapeutic agents for treatment of TBI patients highlights a compelling need to explore and test new drug candidates. We identified two novel compounds that reduce neuronal injury and inflammation; JM6, an experimental neuroprotective drug used in animal models of Alzheimer's and Huntington's disease, and clovanemagnolol, a natural compound with neuro-regenerative properties. Here, we test our hypothesis that the neuroprotective effects of these two compounds are mediated by a common set of genes/ pathways.

Methods: Isoflurane-anesthetized, Male-Sprague Dawley rats (300 to 350 g) received a severe fluid percussion injury. One hour post injury, rats were dosed with JM6 (400 mg/kg oral gavage) or Clovanemagnolol (2 mg/kg IP injection). Reduction of neuronal injury and microglial activation was assessed by Fluoro-Jade C (FJC) staining and immunohistochemistry, with an antibody to CD11b. We used Laser Capture Microdissection to collect neurons from the hippocampal CA1-CA3 regions. Total RNA was sent to GenUs Biosystems for genome-wide microarray analysis (Agilent Rat GE 8x60K arrays). Gene expression data were analyzed with GeneSpring GX and filtered gene lists (>1.5 Fold, $p < 0.05$, Sham vs. TBI, TBI vs. JM6, TBI vs. CM) were uploaded into Ingenuity Pathway Analysis. We validated individual gene changes using Real-Time PCR.

Results: JM6 and Clovanemagnolol significantly ($p < 0.05$) reduced the number of FJC- positive hippocampal neurons and reduced microglial activation in the rat brain. Our analysis showed that JM6 and Clovanemagnolol similarly altered expression of genes that were significantly dysregulated after TBI. The affected pathways (PPAR signaling, axonal guidance signaling and Wnt signaling) are associated with cell survival, synaptic plasticity and development.

Conclusion: JM6 and Clovanemagnolol appear to reduce post-traumatic neurodegeneration by restoring TBI- dysregulated gene expression to sham control levels. Novel drug candidates with similar mechanisms of action could be neuroprotective.

Support: These studies were completed as part of an interdisciplinary research team funded by The Moody Project for Translational Traumatic Brain Injury.

Keywords: Drug

C3 Poster Session V - Group C: Neurocritical Care

C3-01

THE INFLUENCE OF INSURANCE STATUS ON SPINE TRAUMA PATIENT TRANSFERS AT A LEVEL I TRAUMA CENTER WITH A LARGE CATCHMENT AREA

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Introduction: The influence of insurance status upon patient transfers (between Level II/III centers and Level I centers) during certain days of the week for mild head injury has been described in the literature. In this study, we investigate whether there is a relationship between insurance status and the day of transfer for spine trauma patients at one Level I trauma center.

Methods: We reviewed all 734 records of patient transfers to one Level One Trauma Center (Saint Mary's Hospital, Rochester MN) from 2007–2014 for spine trauma. Age, Sex, Race, Marital Status, Insurance Status (Private Insurance, Medicaid, Medicare, Automobile Insurance, Self-Pay), Transferring Hospital Location, Length of Stay, Intervention Performed (egs. fusion, percutaneous vertebroplasty), Admitting Service, Co-Morbidities and Cervical, Thoracic, and Lumbar Spine Trauma (by ICD-9 Diagnostic Codes) were included. STATA software was used for multivariate regression analyses.

Results: We found that transfers on Saturdays for spine trauma requiring intervention is twice as likely if a patient has Medicare than other forms of insurance (OR = 2.0, CI = [1.062–3.813]). Transfers on Mondays for spine trauma requiring intervention is likely not to occur if the patient has Medicare (OR = .394, CI = [.199–.783]) or is privately insured (OR = .408, CI = [.181–.919]). Transfers on the remaining days of the week did not show a significant relationship with insurance status.

Conclusion: In this study of a single Level I Trauma Center over seven years, we found a relationship between insurance status and patient transfer, such that patients on Medicare tend to be transferred out at higher rates on Saturday. The temporal relationship is curious, and may be due to staffing issues at Level II or III centers, or due to gaps in coverage by specialists. If transfers to Level I centers for weekend care are made out of convenience and not necessity, this raises ethical concerns as to where and when optimal patient care should occur.

Keywords: Spine Trauma, Spine Injuries, EMTALA, Patient Transfer, Level I Center

C3-02

TREATMENT OF TRAUMATIC NON-CONVEXITY SUBDURAL HEMORRHAGE IS SIMILAR TO TREATMENT OF TRAUMATIC SUBARACHNOID HEMORRHAGE

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We consider tentorial and interhemispheric subdural hematomas to be non-convexity subdural hematoma (ncSDH) and should proceed with a similar benign course as traumatic subarachnoid hemorrhage (tSAH). Retrospective review of 180 pts who presented acutely to the Emergency Department with intracranial bleeds secondary to trauma found that patients with ncSDH rarely required catheter placement or craniotomy (2 interhemispheric and 0 tentorial). Furthermore, recovery of ncSDH was similar to tSAH. Indications for surgical intervention are generally derived from convexity SDH (cSDH). These criteria include: hematoma volume of ≥30 cc, midline shift of ≥5 mm and presence of neurological signs. However, in elderly populations not exhibiting neurological signs regardless of hematoma volume and midline shift, operative procedures could lead to unnecessary risks and interventions. We hypothesize that the pressure vector generated by ncSDH does not lead to significant pathophysiologic mechanisms, e.g., brain herniation, mass effect, as compared to the more common cSDH. This protection could be conferred by the direction of the pressure exerted against the thick membranes of the falx cerebri and tentorium cerebelli in ncSDH. Furthermore,

the corpus callosum serves as physical restraint for increase in hematoma size. We recommend that conservative and clinical management of ncSDH, be similar to tSAH. The more common cSDH should be distinctly categorized from the ncSDH.

Keywords: Acute traumatic subdural hematoma, Non-Convexity Subdural Hematoma, Tentorial and Hemispheric Subdural Hematoma, Convexity Subdural hematoma

C3-03

EARLY NUTRITIONAL THERAPY AND MINIMAL BLOOD GLUCOSE VARIABILITY IMPROVE OUTCOMES AFTER TBI

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Following severe TBI, dysfunctional cerebral metabolism is associated with metabolic crisis, the coincidence of high cerebral LPR and low glucose, and with poor recovery. Meanwhile, glycemic control in the acute injury period to avoid severe hyperglycemia improves outcomes. The objective of this study was to investigate the impact of nutritive support provided in the neuroICU between post-injury days (PID) 0 and 10 on clinical outcomes, acute glycemic control, and metabolic crisis. Nutritive support (enteral and parenteral routes), point-of-care (POC) glucose, and cerebral microdialysis glucose and LPR were extracted from the UCLA BIRC electronic database and patient charts for twenty-six severely injured consented adults. The variability of clinical data was quantified by the standard deviation of POC glucose readings (recorded approximately every 4 hours), the rate of carbohydrate (CHO) caloric delivery, and insulin provided (bolus and IV) between PID 0-10. Clinical outcomes were Glasgow Outcome Scale extended (GOSe) scores obtained 6 months post-injury. There was a significant correlation between GOSe and kilocalories delivered PID 0 (0.432 [0.054 0.702], $p = 0.028$) but not between GOSe and average daily kilocalories PID 0 through 10 (–0.183 [–0.532 0.220], $p = 0.371$). Additionally, there was a significant negative correlation between GOSe and glucose variability (–0.414 [–0.691 –0.032], $p = 0.035$). Linear modeling significantly predicted GOSe by POC glucose variability ($p = 0.011$), by CHO caloric delivery rate variability ($p = 0.013$), and by total kilocalories received in the first 24 hours following injury ($p = 0.002$). Although the incidence of metabolic crisis was not a significant predictor of GOSe in this cohort, blood-brain glucose correlations PID 0-10 were negatively correlated to incidence of metabolic crisis (–0.406 [–0.690 –0.013], $p = 0.044$). Early nutritional therapy, blood glucose variability and, to a lesser extent, CHO caloric delivery rate variability were predictive of 6 month outcomes. While delivery rate variability was not a significant indicator, the impact of nutritional support, including makeup, timing, and rate of delivery, on glycemic control and variability warrants further research.

Keywords: Glycemia, Microdialysis, 6-month outcome, Neurocritical Care, Nutrition

C3-04

METABOLOMICS OF HUMAN TRAUMATIC BRAIN INJURY

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Understanding metabolomics is paramount in the individualized treatment and prognosis of severe traumatic brain injury (TBI). Analysis of the metabolome has gained significant momentum in this endeavor in numerous disease processes, but has not yet received the attention it deserves in TBI research. As a result, we conducted a preliminary observational and feasibility study aimed at identifying differences in the metabolite composition of TBI patients and normal individuals. Eight subjects, 6 TBI patients (mean age: 31, mean GCS: 3.8) and 2 normal individuals (mean age: 22) were consented and enrolled. Blood samples were collected from all 8 subjects and analyzed using LCMS. We identified a total of 103 metabolites. A principle components analysis revealed a significant separation of the metabolite contributions of TBI versus normal patients in PC2 ($p < 0.0001$). Further investigation revealed that elevations of metabolites of glycolysis and the TCA cycle, such as glycine, lactate, and a-ketogluterate, constituted the unique metabolome of a brain-injured patient. In contrast, citrate, alanine, and phosphoglycerate of these same pathways were elevated in normal individuals. Other differences that were identified between these two groups, included changes in numerous amino acids, neurotransmitters, and metabolites involved in DNA repair. Investigations of the metabolome are of utmost importance in the understanding of post-traumatic metabolism, identification of novel biomarkers, and ultimately improved clinical management of these critically ill patients. While this study is limited by the small number of subjects, it nonetheless demonstrates the feasibility of this methodology and gives a small glimpse into the possibility that this type analysis can offer in directing individualized patient care.

Keywords: Metabolomics, Principal components, Individualized medicine, Energy metabolism

C3-05

USE OF ASPIRIN AND P2Y12 RESPONSE ASSAYS IN DETECTING REVERSAL OF PLATELET DYSFUNCTION CAUSED BY ANTIPLATELET AGENTS IN TBI

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Many adult patients suffering traumatic brain injury have pre-existing comorbidities requiring antiplatelet therapy. These agents potentially worsen outcome, which has resulted in a treatment approach of platelet transfusion in patients with evidence of intracranial bleeding and history of antiplatelet therapy. We seek to understand the utility of the aspirin and P2Y12 response (ARU and PRU, respectively) assays as tools for detecting platelet dysfunction and subsequent reversal following transfusion of platelets in traumatic brain injury patients. Between 2010 and 2015, we conducted a prospective comparative cohort study of patients presenting with a positive head CT and a reported history of antiplatelet therapy. Platelet dysfunction was assessed with the VerifyNow assay (Accumetrics, San Diego, CA) upon admission and 6 hours post-transfusion, with a primary endpoint of disinhibition after platelet transfusion. 107 patients were available for analysis [mean age 75.5 ± 12.2 years, 65% male, median GCS 15 (IQR 13–15) and Marshall score 2 (IQR 2–4)], with 62% taking aspirin, 8% taking clopidogrel, and 30% taking both agents. According to the ARU and

PRU assays, 7% of patients taking any aspirin, and 27% of patients taking clopidogrel were not therapeutic, respectively. After platelet transfusion, 47% of patients on any aspirin and 49% of patients on any clopidogrel failed to be reversed. The ARU increased by 71 ± 76 per unit of platelets, and the PRU increased by 48 ± 46 per unit of platelets. This study provides a means for detecting patients reported to be on antiplatelet agents whom have functioning platelets and receive unnecessary transfusions following a TBI. In addition, a single platelet transfusion may not be sufficient to reverse platelet inhibition in patients who are therapeutic on their antiplatelet therapy. The aspirin and P2Y12 response unit assays have utility in the TBI population and require prospective evaluation as tools for determining whether to transfuse platelets in TBI patients.

Keywords: platelet, aspirin, platelet reactivity, platelet transfusion, clopidogrel

C3-06

TRANSFUSION REVERSAL OF PRE-MORBID ORAL ASPIRIN USE IS NOT PROTECTIVE AGAINST RADIOGRAPHIC PROGRESSION OF INTRACRANIAL PATHOLOGY

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There remains controversy for reversal of antiplatelet agents in traumatic brain injury (TBI) patients. The purpose of this study is to longitudinally evaluate the effect transfusion reversal of antiplatelet agents has on radiographic progression of intracranial pathology. A prospective comparative analysis of TBI patients (>65 years) with evidence of intracranial pathology on computed tomography (CT) scan was conducted at our institution from June 2013-Janurary 2015. We assessed baseline demographics, coagulation parameters, platelet dysfunction using a platelet function assay for aspirin (VerifyNow), transfusion management, and clinical course. The primary endpoint was radiographic progression of intracranial injury defined as expansion of admission pathology using the components ABC/2 method for measuring intracranial lesion. Descriptive data were stratified by having a therapeutic platelet function assay for aspirin on admission, and analyzed via Chi-square test. A total of 96 patients suffering TBI with radiographic intracranial injury and aspirin use were assessed; 86% (83) therapeutic vs 14% (13) sub-therapeutic on aspirin. A logistic regression analysis was performed to compare groups and identify predictors of radiographic progression. Covariates included: age, admission Glasgow coma score (GCS), and baseline Rotterdam scores for CT scan severity. Subgroup multivariate analysis of only those with a therapeutic aspirin response did not demonstrate a significantly different rate of progression in either those being transfused, or those achieving non-therapeutic status post-transfusion (OR = 4.19 (1.37–12.8), p = 0.01). Transfusion reversal of aspirin use was not protective against radiographic progression of intracranial hemorrhage. This data refutes the reflexive transfusion of patients on antiplatelet therapy as a means for therapeutic intervention of aspirin use. Given the latter, the evidence fully supports the need for a randomized clinical trial aimed at identifying an algorithm for platelet transfusion in a subgroup of patients within the TBI population.

Keywords: AntiPlatelets, Transfusions, Hemorrhage Progression

C3-07

INSIGHTS FROM HIGH FREQUENCY INTRACRANIAL PRESSURE DATA: A TREATMENT THRESHOLD BELOW 20MMHG MAY BE MORE APPROPRIATE

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Introduction: Intracranial pressure (ICP) elevation is a compartment syndrome which impairs the flow of blood to the brain. The precise intracranial threshold at which brain injury begins to occur remains uncertain.

Methods: A computer system automatically collected and stored q1 minute physiological data from ICU patients over a 6 y period. Data for 516 patients who underwent ICP monitoring was collected, 372 of whom had a traumatic brain injury; outcome data (GOS) was available for all but 19. Mean ICP was calculated for epochs up to 30d from the start of intensive care. The proportion of ICP values above thresholds from 1 mmHg to 80 mmHg in were calculated in 1 mmHg increments for these same epochs. The relationship between these measures and outcome was explored. A complementary principal component analysis (PCA) was used to explore physiologic changes at various ICP thresholds.

Results: A total of 4,090,964 q1 minute ICP measurements were recorded for the included patients (7.78 patient years of recordings). 8.9% and 3.7% were above 20 and 25 mmHg respectively. Mean ICP values correlated with outcome for 14d after admission. ICP values below 20 mmHg were associated with outcome and time spent above ICPs from 17 to 19 seemed most strongly associated with outcome. The PCA suggested physiologic changes above intracranial pressures of 19 mmHg and 24 mmHg.

Conclusions: This study provides strong evidence supporting a correlation between ICP values and outcome but does not provide evidence of a causal relationship. It suggests that ICP values below 20 mmHg may be harmful and that ICP might best be kept lower than 19 mmHg.

Keywords: treatment threshold, high frequency, physiology, neuromonitoring

C3-08

PATIENTS WITH SPINAL CORD INJURIES FAVOR ADMINISTRATION OF METHYLPREDNISOLONE BUT HAVE LITTLE INPUT INTO ITS ADMINISTRATION

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Object: The use of methylprednisolone sodium succinate (MPSS) for acute spinal cord injury (SCI) is associated with small functional benefits and elevated risk of adverse events. We sought to learn the opinions and preferences of SCI patients regarding MPSS as well as their involvement in the decision to administer MPSS.

Methods: 27 SCI experts adjudicated a document summarizing the literature regarding MPSS use in acute SCI. They rated it neutral,

non-biased, and of acceptable quality. This datasheet and an online questionnaire were then emailed to 384 patients with chronic traumatic SCI. The chi-square test was used to analyze responses.

Results: 77 patients completed our questionnaire (20.1%). 65 of the 77 patients (84.4%) report arriving to the hospital within the 8 hour MPSS treatment window. Only 6 patients (7.8%) reported that they were given the chance to decide whether they would receive MPSS or not. Only 11 patients (15.3%) know whether they received MPSS or not.

59.4% of respondents rated the small neurological benefits associated with MPSS as being very important to them (10 on a 10 point Likert scale, $p < 0.0001$). Patients had little concern for potential side-effects of MPSS (49.3% chose 1–3 on a 10 point Likert scale, $p < 0.0001$). The majority of patients (53.2% or 41/77) ''felt strongly'' that MPSS should be a treatment option for SCI patients ($p < 0.0001$). Only 1.4% of respondents felt that MPSS should not be given to SCI patients ($p < 0.0001$).

Conclusion: Communication surrounding MPSS administration was poor. Patients with SCI favor the administration of MPSS for acute SCI, however very few had input into whether or not it was administered. Conscious patients should be given greater opportunity to decide how they are treated; the results of this study provide some guidance regarding MPSS administration in patients who are unable to communicate.

Keywords: methylprednisolone, spinal cord injury, patient preference, communication

C3-09

IMPLEMENTATION OF UNIQUE PROCESS FOR CEREBRAL MICRODIALYSIS AT A LEVEL I TRAUMA CENTER

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Objectives: To create an efficient and reliable process for cerebral microdialysis (CMD) promoting rapid speciment turnaround and optimal utilization of multidisciplinary organizational roles.

Background: Industry implementation of cerebral microdialysis includes point of care bedside analysis of hourly microdialysis specimens. Establishing a unique process using a collaborative multidisciplinary team approach at our level I trauma hospital, microdialysis specimen analysis is processed in the clinical laboratory. This unique process promotes nurses' role to focus on vigilant patient assessment, monitoring, and implementation of therapies to prevent secondary brain injury.

Methods: Planning initiated in the third quarter 2012 with implementation in April 2013. Specific roles and process steps were established for team members. Handoff of microdialysis specimens in the trauma intensive care unit reflects time of patient specimen removal to courier handoff for hand delivery to the STAT clinical laboratory for immediate analysis. Handoff tools provide quality improvement data for monitoring and team communication.

Results: The process improved teamwork, communication and resource utilization. The mean delivery to lab time = 5.5 minutes for 98 CMD patients since initiation of the process. Successful process eliminated need for nurses to perform point of care lab analysis on microdialysis specimens. Process demonstrates effective communication and matches team member roles according to training and expertise.

Conclusions: Creating a process with specific roles matched to organizational roles improved specific process, efficiency, and communication. Clarifying roles and responsibilities can reduce time to interventions and improve outcomes.

Keywords: Microdialysis, Specimen processing, Multidisciplinary implementation

C4 Poster Session V - Group C: Neurotoxicity/ Neuroexcitation

C4-01

NEUROLOGICAL COMPLICATIONS DUE TO A SUBARACHNOID INJECTION OF HYPERTONIC CONTRAST MEDIA IN RAT

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Myelography is routinely performed using a non-ionic contrast media. However, the inadvertent administration of ionic hypertonic contrast media into the subarachnoid space results in convulsions and acute respiratory failure, and can lead to death if not treated immediately. The mechanisms underlying the adverse effects of hypertonic contrast media on the central nervous system are unclear. We examined the effects of a subarachnoid injection of hypertonic contrast media (60% Urografin®; osmotic pressure 6) on the central nervous system in the rat. Under general anesthesia, rats were administered a subarachnoid injection of 20.0, 10.0, 7.5, or 5.0 μL of Urografin® or saline. The rats that received 20.0 or 10.0 μL of Urografin® immediately developed severe convulsions and died within 42 minutes of the injection. The rats that received 7.5 or 5.0 μL of Urografin® exhibited delayed-onset convulsions that subsided within 240 minutes. Immunohistological examinations of the brain and spinal cord two days after the 7.5 μL Urografin® injection revealed microglial activation and decreased expression of transient receptor potential vanilloid 4 (TRPV4), a protein related to osmoregulation, in the brain stem. Neither convulsions nor histological changes were observed in rats that received the saline injection. These findings indicate that the extent and duration of convulsions and fatality depend on the volume of hypertonic contrast media. Furthermore, brain stem injury is the mechanism underlying the acute respiratory failure that occurs following the subarachnoid injection of hypertonic contrast media. This study also suggests that high cerebrospinal fluid osmolality affects the central nervous system.

Keywords: cerebrospinal fluid, osmotic pressure, microglia, transient receptor potential vanilloid 4 (TRPV4), contrast media, myelography

C4-02

ALTERED TRYPTOPHAN METABOLISM IN BLAST-INDUCED TRAUMATIC BRAIN INJURY

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Blast-induced traumatic brain injury (bTBI) is one of the major disabilities in service members returning from recent military operations. The neurobiological underpinnings of bTBI, which is associated with acute and chronic neuropathological and neurobehavioral deficits, are uncertain. The role of the essential amino acid, tryptophan, in the

pathogenesis of bTBI has not been explored. We have reported earlier that blast exposure causes significant decrease in the levels of the neurotransmitter and tryptophan metabolite serotonin, which has been implicated in affective disorders such as depression and anxiety. Our preliminary studies using rat and mouse models of single and repeated bTBI utilizing a compressed air-driven shock tube revealed up-regulation of indoleamine 2,3-dioxygenase (IDO1), in different regions of the brain which increased with repeated blast exposures. This up-regulation of IDO1 after blast exposure, which may be an endogenous immunosuppressive protective mechanism mediated through the kynurenine pathway, could account for decreased levels of serotonin. Blast exposure also acutely increased expression of IDO1 in the spleen and the expression was further elevated with repeated blast exposures, which by depleting circulating tryptophan can decrease synthesis of serotonin. These results reveal that systemic and central tryptophan metabolism are disrupted following blast exposure which might play a significant role in the pathogenesis of neurobehavioral deficits associated with bTBI.

Keywords: Traumatic brain injury, Blast exposure, Tryptophan, Serotonin, Indoleamine 2,3-dioxygenase

C5 Poster Session V - Group C: Pain

C5-01

MORPHINE TREATMENT AFTER TBI EXACERBATES COGNITIVE IMPAIRMENTS AND REDUCES NEURONAL SURVIVAL IN A RAT MODEL

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The most commonly used treatment for pain after Traumatic Brain injury (TBI) is morphine (Bratton el al., J. Neurotrauma 24:S1 pS71, 2007). This treatment meets a critical need for alleviating the severe pain typically accompanying TBI. However, morphine has several well-known adverse effects including some particularly relevant to TBI. In the short-term, respiratory depression can cause increased CO_2 and intracranial pressure. In the long term, a lesser known side effect, a proinflammatory response (Hutchinson et al., Pharmacol Rev 63:772, 2011) could exacerbate long-term secondary neuropathological sequelae of TBI (Bachstetter et al., J Neurosci **33**: 6143, 2013). Here we tested the effects of 3-day infusion of morphine beginning 24 hr *after* fluid percussion TBI on subsequent cognitive and neuronal changes. The post-TBI treatment paradigm was chosen over typical pre- or concurrent treatment paradigms for clinical relevance. Morphine exacerbated TBI-induced impairment of spatial memory acquisition during a standard 5-day Morris Water Maze (MWM) training test. In 1-day and multiday reversal tests, TBI + morphine impaired learning of a new position of the escape platform. Following the behavioral tests, immunohistochemical analyses were conducted and showed that TBI + morphine decreased NeuN-labeled neurons in the molecular layer of the dentate gyrus of the hippocampus and in the reticular nucleus of thalamus. Changes in both of these areas are considered major contributors to the pathophysiological effects of TBI. The results indicate an unmet need for novel treatments for TBI pain with the effectiveness of morphine but without the associated respiratory and pro-inflammatory effects that can exacerbate subsequent cognitive and neuronal pathologies.

Supported by the VA and DOD
Keywords: Spatial Memory, Morphine

C5-02

TRAUMATIC BRAIN INJURY IN MICE INDUCES CHRONIC HYPERESTHESIA

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Clinical studies indicate that traumatic brain injury (TBI) patients frequently experience chronic post-traumatic pain, particularly vascular-type headache. Although headache descriptions predominate, patients may also experience allodynia, hyperesthesia, or spontaneous pain. Periorbital and extra-cephalic (paw) mechanical allodynia have been reported in rodent models of TBI, which may persist for weeks after injury. However, there has been little research devoted to understanding the pathobiology to such hyperesthesia. The present study characterized post-TBI sensory changes in mice with mild, moderate or severe controlled cortical impact injury (CCI) by testing mechanical/thermal allodynia, as well as presence of spontaneously face pain. C57BL/6 male mice were subjected to mild, moderate, or severe CCI and mechanical/thermal allodynia as well as mouse grimace scale (MGS) test, a measure of spontaneous pain, were evaluated before and after TBI. The von Frey hair force was significantly decreased on the left hindpaw of mice subjected to moderate or severe TBI when compared to sham operated mice. On the right hindpaw, a significant decreased force was observed in the mice with moderate TBI. The threshold for hot plate temperature was decreased in a severity-dependent manner. The threshold for cold plate was significantly increased in the mice subjected to all grades of TBI severity at early time points (week 1 and 2) but returned to baseline level at 4 weeks post-injury. MGS based on ear position, orbital tightening, and nose bulge was transiently increased at post- TBI day 1 for all groups. Sham and mild TBI group returns to the baseline level at week 1. However, moderate and severe TBI mice showed extended increases of MGS. The present study characterizes the time course of hyperesthesia after TBI of varying severity. These observations indicate that more generalized hyperesthesia and pain, as well as vascular-like headaches, may occur after TBI, and may serve as a model to characterize the pathobiology and potential therapies for such pain.

Keywords: traumatic brain injury, hyperesthesia, mechanical/thermal stimulation, the mouse grimace scale, pain

C5-03

CELL CYCLE ACTIVATION CONTRIBUTES TO DEVELOPMENT AND MAINTENANCE OF NEUROPATHIC PAIN FOLLOWING SPINAL CORD INJURY

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In addition to causing sensorimotor deficits, spinal cord injury (SCI) also results in posttraumatic neuropathic pain in a majority of patients.

Chronic pain after SCI may present as hyperalgesia, allodynia, and/or spontaneous pain and is often resistant to conventional pain therapy. Identifying better interventions to manage SCI-PAIN requires improved understanding of the pathophysiological mechanisms involved. After SCI, a key pathophysiological mechanism appears to be cell cycle activation (CCA). We have shown previously that central or systemic early administration of a selective CCA inhibitor reduced CCA, glial changes, and limited SCI-induced hyperesthesia. Here we compared the effects of early versus late treatment with pan-CDK inhibitor flavopiridol on allodynia as well as presence of spontaneously face pain. Adult C57BL/6 male mice subjected to moderate SCI were treated with daily IP injections of flavopiridol (1 mg/kg), beginning 3 h or 5 weeks after injury and continually for 7 days, mechanical/thermal allodynia as well as mouse grimace scale (MGS) test, a measure of spontaneous pain, were evaluated. We showed that the von Frey hair force, thresholds response to thermal stimulation, and locomotor function were significant improved in early flavopiridol-treated mice when compared to vehicle group. MGS based on ear position, orbital tightening, and nose bulge was transiently increased at day 1 post-injury for all groups. The mice with SCI showed robust and extended increases of MGS up to 3 weeks. Early administration of flavopiridol significantly reduced MGS at week 1 and returned to the baseline level at week 2. Late flavopiridol injection significantly limited hyperesthesia at 7 days after treatment with no effects on locomotion. Thus, our data suggest that cell cycle modulation may provide an effective therapeutic strategy to improve reduce both hyperesthesia and motor dysfunction after SCI. These findings would also markedly expand the potential therapeutic window for such pain.

Keywords: spinal cord injury, hyperesthesia, mechanical/thermal stimulation, the mouse grimace scale, neuropathic pain

C6 Poster Session VI - Group C: Electophysiology

C6-01

DELAYED PRIMARY BLAST-INDUCED ELIMINATION OF LONG-TERM POTENTIATION IN RAT ORGANOTYPIC HIPPOCAMPAL SLICE CULTURES

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Blast-induced traumatic brain injury (TBI) is the signature wound of the conflicts in Iraq and Afghanistan. This study investigated the time-course of primary blast loading on electrophysiological function within rat organotypic hippocampal slice cultures. Blast injury was initiated with a compressed-gas driven shock tube. Electrophysiological recordings were acquired at either 60 minutes, 1, 2, 4, 6, or 10 days following injury using 60-channel microelectrode arrays. Functional recordings were collected following either a sham, mild (336 kPa/0.84 ms/87 kPa·ms) or moderate injury (424 kPa/2.31 ms/248 kPa·ms). Long-term potentiation was induced in CA1, via the Schaffer collateral pathway, using 100 Hz tetanic current stimuli. LTP induction was calculated as percent potentiation above baseline based on the last 10 minutes of pre- and post-induction baseline recordings. We observed that neither blast level reduced LTP at 1 hour post-injury; however, both blast intensities significantly reduced LTP between 1 and 6 days post-injury. LTP recovered in mild blast-exposed cultures at 10 days post-injury, but not in moderate blast exposed cultures. We conclude that primary blast injury does not eliminate LTP immediately post-injury, but rather between 1 and 24 hours after injury. There is potential for natural recovery of LTP following blast, but only at 10 days following a mild blast exposure. LTP deficits may be the source of memory loss commonly observed in TBI patients. Future research will elucidate the cellular mechanisms responsible for this delayed disruption of LTP following primary blast injury.

Keywords: Blast, TBI, In Vitro, Electrophysiology, Hippocampus

C6-02

EFFECT TBI ON SLEEP AFTER LATERAL FLUID-PERCUSSION INJURY IN RATS

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Introduction: Transitional stage between wakefulness and non-REM sleep is the period when the brain is most prone for generating epileptic seizures whereas REM sleep is the most antiepileptic state of the sleep-wake cycle. Our objective was to test a hypothesis that the occurrence of spike-and-wave discharges (SWDs), present in a subpopulation of rats, affects the sleep architecture after TBI.

Methodology: TBI was induced with lateral fluid-percussion injury (FPI) in 12 adult Spraque-Dawley rats. Eleven sham-operated rats served as controls. Starting at 7 months post-TBI, animals were continuously video-EEG monitored to assess sleep. A 24-h continuous EEG recording was divided in 2947 epochs (30 sec each), and scored according to the recommendations American Academy of Sleep Medicine (2007) with slight modifications. Sleep pattern was analyzed separately during lights-on and lights-off periods.

Results: When all animals with TBI or sham-operation were compared, we found no differences in S2, S3, REM, or wake stages. When rats with (SWD+) or without (SWD-) SWDs were analyzed separately, we found that during lights-off period the TBI-SWD+ group ($n=9$) spent less time in REM sleep than the TBI-SWD- ($n=3$) (61%, $p=0.02$) or the control-SWD+ group ($n=3$)(82%, $p=0.03$). Similarly, the control-SWD+ group ($n=8$) showed reduced REM sleep during lights-off period as compared to control-SWD- group (74%, $p=0.05$). The duration of stage II ($p>0.05$) or stage III ($p>0.05$) sleep did not differ between any of the TBI and control groups. Analysis of hypnograms revealed that the architecture of sleep was less structured in rats TBI than in controls.

Conclusion: Our data show that occurrence of SWDs is associated with reduced REM sleep both in controls and TBI animals during lights-off period, and the effect is even more pronounced after TBI. These data suggest that cortico-thalamic activity, driving the SWDs, modulates sleep architecture during the lights-off period.

Keywords: Sleep, Circadian Rhythm, spike-and-wave discharges, TBI

C6-03

ELECTROPHYSIOLOGICAL PHENOTYPING OF HUMAN NEURONS IN SLICES AND DISSOCIATED CULTURE

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The electrophysiological and morphological phenotyping of human neurons was performed on resected cortical and hippocampal tissue from cases of Communicating Hydrocephalus, Epilepsy, Normal Pressure Hydrocephalus and brain tumor. A clinical history of traumatic brain injury (TBI) was present in a number of these cases. The differences in electrophysiological properties of adult human neurons are being correlated to the single-cell analysis of the mRNA transcriptome. With IRB approval 73 patients were enrolled with informed consent, with several having a history of TBI (age 25–86). A case report form was populated with the subject information, which includes cortical location of the tissue, past medical history and pathology report. Brain tissue that is otherwise discarded was collected into ice-cold oxygenated artificial cerebrospinal solution to preserve the cortical circuitry components. We developed a methodology to electrophysiologically characterize neurons from both acute brain slices and primary neuronal cultures. Spontaneous and induced action potentials as well as concurrent field potentials were recorded from 350 um thick cortical and hippocampal slices using intracellular sharp electrodes filled with potassium acetate. Dissociated adult human neurons survived in culture for over 6 weeks. In order to electrophysiologically characterize cultured neurons, whole-cell currents and action potentials were recorded using patch-clamp technique, and intrinsic membrane properties such as input resistance and membrane potential were analyzed. Sequencing of the transcriptome for a subset of these neurons is in process, and will allow for correlation of the variability in the electrophysiological properties with mRNA expression. In order to develop a better understanding of the variability of the mRNA profile of individual cells, as well as in various disease states, identified correlations will be compared between TBI and non-TBI cases.

Keywords: TBI, adult human neurons, electrophysiology, single cell mRNA analysis

C6-04

TIME-COURSE PROFILE OF EEG ABNORMALITY DETECTED BY QEEG POWER SPECTRAL ANALYSIS FOLLOWING A SINGLE CONCUSSIVE BRAIN INJURY IN RATS

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Quantitative EEG (qEEG) is a sensitive measure of cerebral functional changes following brain injury. In this study we applied qEEG power spectral analysis to examine EEG power shifts caused by a mild concussive brain injury. Rats received a single projectile concussive impact (PCI) injury aimed at the right dorsal surface of the brain, or sham procedures, immediately followed by bilateral EEG electrode implantation and continuous EEG monitoring for 14 days. The qEEG power spectral analysis was performed at 6, 12, 18, 24, 48, 72h, 7, and 14 days post-injury. The EEG global frequency band was divided into standard delta, theta, alpha, beta, and gamma bands. The relative EEG power of each band was expressed as the percent of the total power of the global band. Spectral power analysis revealed that moderate but significant EEG slowing occurred as early as 6h post injury in the ipsilateral hemisphere, which persisted for at least 24h as evidenced by a significant increase in EEG delta power ($p < 0.05$ vs. sham at each time point). Similar trends in EEG slowing, albeit to a lesser degree, were measured between 48 and 72h post PCI ($p > 0.05$), followed by the restoration of normal EEG activities by the 7th day post PCI which remained stable thereafter. EEG slowing in the contralateral hemisphere was manifested in a delayed and more transient fashion, with mirrored increases in the delta activity only at 18 and 24h post PCI without the subsequent tapering phenomenon observed in the ipsilateral hemisphere. In summary, the demonstration of EEG slowing in the rat model of mild concussive brain injury provides a functional brain injury marker which can be used along with other biological and behavioral measures to better understand the pathological mechanisms of concussive brain injury.

Keywords: EEG Power Spectrum Analysis, Projectile Concussive Impact Brain Injury, Rats

C7 Poster Session VI - Group C: Inflammation

C7-01

MORPHOLOGY ALONE DOES NOT DEFINE THE RANGE OF MICROGLIAL PHENOTYPES AFTER DIFFUSE BRAIN INJURY

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Microglial activity affects neurological function. Ramified microglia represent a naïve state; whereas activated microglia, in varying proportions of morphologies, indicate states of disease. Identifying cellular markers associated with each microglial morphology may more precisely define microglial function. Here, we demonstrate that morphologically similar microglia do not necessarily have similar patterns of cellular markers. Adult male Sprague-Dawley rats were subjected to midline fluid percussion sham or brain-injury. Brain tissue was collected at 2h, 1d, 2d, 7d, 28d and 56d post-injury. To characterize the phenotype of microglia, immunohistochemical double-labelling was undertaken with Iba1 in conjunction with CD45, CD68 (ED1), CD11b, or Ox6 (MHCII). Analysis concentrated on the sensorimotor cortex. Iba1 positive ramified microglia did not show reactivity to CD45 or CD68. Injury-induced microglial activation included Iba1-positive activated, amoeboid and rod microglia. When amoeboid microglia were present, they were reactive for CD45, however no other morphology reacted with this marker. For CD68, no microglial morphology showed reactivity at 2h post-injury. By 1d post-injury, some activated and amoeboid microglia showed reactivity, but rod microglia did not. At 7d, in addition to activated and amoeboid microglia, some but not all, rod microglia showed CD68 reactivity. By 28d post-injury, CD68 reactivity had increased predominantly in activated and amoeboid microglia. Furthermore, Ox6 was present in some, but not all, activated and rod microglia at 7d. Intriguingly, not all rod microglia reacted to Ox6 despite these cells appearing to be coupled. These data indicate an over simplification in relying on morphology for microglial activation state. Studies inevitably need to combine morphology and cytokine receptor levels to more accurately phenotype microglia, for which specific functions have yet to be ascribed. Moreover, precision medicine could manipulate microglial phenotypes to restore neurological function. Partially supported by NIH NINDS R01NS065052 and PCH Mission Support Funds.

Keywords: Microglia, Diffuse brain injury, Immunohistochemistry

C7-02

OMEGA-3 DERIVED LIPID MEDIATORS DIFFERENTIALLY IMPACT FUNCTIONAL OUTCOME, SLEEP, AND MICROGLIAL ACTIVATION AFTER EXPERIMENTAL TBI

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Traumatic brain injury (TBI) initiates a cascade of secondary injury processes, including inflammation. Therapies which resolve the inflammatory response may promote neural repair without exacerbating injury. Omega-3 fatty acids, including docosahexaenoic acid (DHA), have shown efficacy in improving outcome from experimental TBI with little known regarding specific mechanisms. Endogenous lipid mediator derivatives of omega-3 fatty acids termed resolvins have recently been characterized in the active resolution of peripheral inflammation. We hypothesized that administration of exogenous resolvins RvE1 or AT-RvD1 would alleviate injury-induced post-traumatic sleep and functional impairments through modulation of inflammation. Experimental groups included midline FPI brain-injured mice administered RvE1, AT-RvD1, or saline and counterbalanced with sham mice. Resolvins or saline were administered intraperitoneally for seven days beginning 3 days prior to TBI. Immediately following TBI, sleep was monitored for 24 hours. Sensorimotor outcome was assessed by rotarod 1–7 days post-injury (DPI). Cognitive function was evaluated using novel object recognition (NOR) at 6DPI. At 7DPI, morphological activation of microglia was semi-quantified using Iba-1 immunolabeling. AT-RvD1, but not RvE1, treatment mitigated motor and cognitive deficits. RvE1 treatment significantly increased post-traumatic sleep compared to all other groups and RvE1-treated mice displayed a lower proportion of activated rod microglia in the cortex compared to other brain-injured groups. Due to this convergence in efficacy, AT-RvD1 may impart functional benefit through mechanisms other than resolving inflammation. AT-RvD1, a derivative of DHA, may contribute to the therapeutic efficacy of omega-3 fatty acids following CNS trauma. Future studies will explore therapies to increase the availability of endogenous resolvins after injury.

Support: Bruce and Diane Halle Foundation, NIH R21-NS072611
Keywords: traumatic brain injury, resolvin, behavior, mouse, inflammation

C7-03

POST-TRAUMATIC SLEEP AS A BIOINDICATOR OF INFLAMMATION: NOVEL TNF-R INHIBITORS RESTORE FUNCTION FOLLOWING EXPERIMENTAL TBI

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Diffuse traumatic brain injury (TBI) acutely increases sleep in the mouse. During this acute window of post-traumatic sleep, cortical levels of inflammatory cytokines, including tumor necrosis factor (TNF), are significantly increased, suggesting a relationship between sleep and inflammation. Here, we hypothesize that post-traumatic sleep serves as a bioindicator of injury-induced inflammation to screen novel therapeutics for efficacy in promoting neurological recovery from TBI. Novel inhibitors of TNF receptor (TNF-R) activation were synthesized and screened for *in vitro* efficacy of TNF pathway inhibition (IkB-phosphorylation). Then, candidate compounds were screened for *in vivo* efficacy in modulating post-traumatic sleep. Mice (n = 33) were subjected to sham or diffuse brain injury (midline-FPI). Cohorts received novel TNF-R inhibitors (Compound-7;SGT11;F002) or vehicle intraperitoneally immediately following injury. Sleep was recorded via non-invasive cages. Over 6 hours post-injury, brain-injured vehicle-treated mice slept significantly more than sham mice ($F(1,11) = 6.8; p = 0.02$). Brain-injured mice treated with Compound-7 ($F(1,8) = 5.4; p = 0.04$) or SGT11 ($F(1,7) = 7.7; p = 0.03$) slept significantly less than vehicle-treated mice, suggesting a therapeutic potential. Compounds were then tested for efficacy in improving functional recovery (n = 38). SGT11 restored sensorimotor (rotarod;($F(3,34) = 6.6; p = 0.001$) and neurological function (modified neurological severity score;($F(3,34) = 4.1; p = 0.01$). Cognitive function (novel object recognition) was restored by both SGT11 ($t(18) = 2.17; p = 0.0143$) and Compound-7 ($t(14) = 2.196; p = 0.0454$). Injury-induced increases in cortical microglial activation were evident for all treatments. Compound-7 and SGT significantly decreased cortical inflammatory cytokines 3 hrs post-TBI (n = 24). In summary, post-traumatic sleep served as an effective bioindicator to screen novel compounds for the treatment of experimental TBI. In summary, pharmacological inhibition of the TNF pathway accelerated recovery of function following TBI and measurement of post-traumatic sleep may facilitate precision medicine through the identification of therapeutic candidates for neurological injury.

Funding: NIH-NINDS-R21-NS072611, SfAZ
Keywords: TBI, TNF, sleep, novel therapeutics

C7-04

IMMUNE-MODULATORY HYDROGEL CARRIERS FOR STEM CELL THERAPY AFTER TRAUMATIC BRAIN INJURY

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Traumatic Brain Injury (TBI) is a serious clinical problem that affects 1.7 million Americans annually. Neural stem cell (NSC) transplantation is a promising treatment for TBI, which is characterized by neuronal loss. However, poor cell survival post-transplantation hinders potential gains. A major contributor to the survival of NSCs is the response of the immune system that recognizes the transplanted cells causing active rejection. Currently, experiments investigating the effect of human neural stem cells on rodent models of brain injury require the use of immune-deficient animals or systemic immune-suppression. In this study, we test the hypothesis that Fas ligand (FasL), a apoptosis inducing ligand against host T cells, will engender localized immune-suppression at the site of NSC transplantation and result in

enhanced survival of NSC. We used a controlled cortical impact device to perform a TBI on immune-competent rats. Human NSCs were transplanted into the rats 2 days after injury using FasL releasing agarose hydrogels. The ability of FasL releasing hydrogels to induce T-cell apoptosis and enhance NSC survival was analyzed 2 and 4 weeks after injury (n = 5 per animal group at each time point). Human NSC injections using cell media or agarose hydrogels were used as controls. We found a significant enhancement of CD8 + T cells expressing the apoptosis marker caspase 8 in the rats injected with FasL releasing hydrogels in comparison to the control groups at 2 weeks post-injury. Furthermore, the rats injected with FasL releasing hydrogels showed an increase in the survival of human NSC at 2 and 4 weeks post-injury. These results suggest that the FasL releasing hydrogels were successful creating an immune-privileged zone around the NSC transplantation site. The development of cell carrier strategies to induce localized immune-suppression represents a novel approach to enhancing the survival and efficacy of stem cell transplantation without systemically affecting the patients' immune system.

Keywords: Immune-suppression, xenografts, neural stem cell, Traumatic brain injury

C7-05

ANALYSIS OF IBA-1 AND INFLAMMATORY RESPONSE IN YOUNG ADULT MICE AFTER MILD TRAUMATIC BRAIN INJURY

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Mild traumatic brain injury (mTBI) makes up 70–80% of all TBI cases in the USA. While mTBI's deficits are often subtle, many patients experience long-term neurological, cognitive, and behavioral problems following injury. This study highlights the imperative need to reduce the consequences of mTBI by examining the inflammatory response and upregulation of the ionized calcium-binding adaptor molecule 1 (Iba-1) in activated microglia. A mouse model of mTBI was used to measure Iba-1 levels in various brain regions to determine the specific time point, location and severity of inflammation.

Anesthetized male young adult mice were administered a mild, midline impact over intact skull and sham surgery was used as a control. Brains were harvested at 6, 24, 48, and 72-hours, and 7-day time points post-injury (n = 3 per time point) and tissues prepared for immunohistochemistry using antibodies against Iba-1.

Qualitative analysis was completed through the examination of the morphological state of the microglia identified by positive Iba-1 staining. Microglia were classified as ramified (spiny) as unactivated or amoeboid (smooth) as activated microglia. The degree of inflammation was categorized as + (mild), ++ (moderate), and +++ (severe) and the state of activated response was measured.

Analysis established the greatest activated response occurred between 24 and 48-hours in mTBI mice. At these time points the impact site, arcuate nucleus, and optic tract demonstrated the highest degrees of inflammation in mTBI mice when compared with sham controls. Also at the same time point, the nucleus accumbens, corpus callosum, caudate putamen, and cortex demonstrated a moderate response when compared with sham controls. The initial point of increase in microglia activation was noted at the 24-hour time point, except the optic tract, which had a robust response at the 6-hour time point. The data may suggest parameters for a therapeutic window, where targeted reduction in inflammation may limit the effects of mTBI.

Keywords: mTBI, Iba-1, inflammatory response, immunohistochemistry

C7-06

PERIPHERAL IMMUNE RESPONSE AFTER PEDIATRIC TRAUMATIC BRAIN INJURY IN RABBIT

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Background: Increased levels of inflammatory cytokines and biomarkers from the cerebral spinal fluid and brain have been found following traumatic brain injury (TBI) in humans and in animal models. However, inflammatory changes outside the brain in the peripheral immune system after TBI are less well studied. More specifically, the peripheral inflammatory response in pediatric TBI remains largely unknown.

Objective: To define changes in pro and anti-inflammatory processes in the peripheral immune system in the acute and sub-acute time period following pediatric TBI.

Methods: Rabbit kits (n = 64) from the same litter were randomly divided into naïve (no intervention), sham (craniotomy alone), and TBI (controlled cortical impact; 6 mm impactor tip; 5.5 m/s, 2 mm depth) groups. Spleens and peripheral blood were collected at 6 hrs, 1 day, 3 days, and 7 days post-injury. The mRNA levels of TNF-alpha, IL1-Beta, IL10, IL-4, IL-6, YM1 and TGF-beta in the spleens and peripheral blood were analyzed by real-time PCR. Spleens also underwent immunohistochemical analysis for presence and quantification of inflammatory cells.

Results: Results show a decrease in anti-inflammatory cytokines present in the TBI spleens at 6 hr and 1 day with no significant change in pro-inflammatory cytokines, compared with naïve and sham groups. YM1 was found to be significantly increased in spleens 7 days post injury. Aside from YM1, no change in pro or anti-inflammatory cytokines was noted in the spleens at 3 or 7 days post injury.

Conclusion: The response of the pediatric peripheral immune system to TBI is differentially regulated following insult. Anti-inflammatory cytokines circulating peripherally appear to preferentially attenuate in the acute period post TBI. Recognition of these alterations in the peripheral immune system may direct peripherally administered therapies and testing for TBI in the future.

Keywords: traumatic brain injury, spleen, cytokine, inflammation

C7-07

NEUROINFLAMMATION IN A RABBIT MODEL OF PEDIATRIC TRAUMATIC BRAIN INJURY

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Neuroinflammation following TBI is a major player in the secondary response post-injury contributing to widespread cell death and tissue loss. Microglial distribution and function in the developing brain plays an important role in the inflammatory response following TBI in the immature brain. In this study, we evaluated the sequential inflammatory

responses, as well as inflammation-induced changes in tryptophan-kynurenine pathway in a rabbit pediatric TBI model. On postnatal day 5–7 (P5-7), New Zealand white rabbits from the same litter were randomized into three groups, naïve (no injury), sham (craniotomy alone) and TBI (controlled cortical impact [CCI]: 6 mm impactor tip; 5.5 m/s, 2 mm depth, 50 msec duration). Animals were sacrificed at 6h, 1, 3, 7 and 21 days post-injury for evaluating mRNA and protein expressions of pro- and anti-inflammatory cytokines, as well as the major components in the tryptophan-kynurenine and glutamate pathways. Myelination was evaluated by myelin basic protein (MBP) staining. We found that the pro- and anti-inflammatory cytokines levels were differentially regulated in a time-dependent manner post-injury. Peak expression of TNF-α and IL-10 occurred 3 days after injury. However, IL1-β expression was upregulated throughout the evaluation period. This was associated with increased expression of Indoleamine 2,3 dioxygeenase (IDO) the rate limiting enzyme in the tryptophan-kynurenine pathway, that is up-regulated by pro-inflammatory cytokines, suggesting the shift of tryptophan metabolism away from serotonin towards the kynurenine pathway. A decrease in myelination in both ipsilateral and contralateral hemispheres was noted 21 days after TBI and may be related to the ongoing pro-inflammatory microglial presence in the white matter tracts in the developing brain leading to secondary axonal or oligodendrocyte injury. A better understanding of the timing of the inflammatory response and its role in injury and repair following TBI is crucial for appropriately designing and evaluating neuroprotective therapies in pediatric TBI.

Keywords: traumatic brain injury, Neuroinflammation, rabbit, cytokines

C7-08

ACCUMULATING BETA-AMYLOID ALTERS THE POST-INJURY INFLAMMATORY RESPONSE

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Traumatic brain injury (TBI) has acute and chronic sequelae, including an increased risk for the development of Alzheimer's disease (AD). Recent studies have implicated beta-amyloid as a major manipulator of the inflammatory response. To examine neuroinflammation following TBI and development of AD-like features, these studies examined the effects of TBI in the presence and absence of beta-amyloid. The R1.40 mouse model of cerebral amyloidosis was utilized. Unexpectedly, in R1.40 mice the acute neuroinflammatory response to TBI was strikingly muted, with reduced numbers of CNS myeloid cells acquiring a macrophage phenotype. However, at chronic time points, R1.40 mice exhibited enhanced brain cavitation, relatively unchanged levels of macrophage activation with enhanced genotype-dependent cytokine expression, and task-specific worsening of cognitive function compared to Non-Tg mice. These findings suggest that accumulating beta-amyloid in the R1.40 mouse model leads to a reduced post-injury macrophage response, persistent neuropathological deficits, and altered cognitive status. Together, these studies emphasize the role of post-injury neuroinflammation in modulating long-term sequelae following TBI and also support recent studies implicating beta-amyloid as a modulator of the neuroinflammatory response.

Keywords: beta-amyloid, macrophage, Alzheimer's disease, neuroinflammation

C7-09

THE ADAPTIVE IMMUNE RESPONSE IN THE BRAIN CORRELATES WITH LONG-TERM NEUROLOGICAL DYSFUNCTION IN A MOUSE MODEL OF TBI

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Traumatic brain injury (TBI) causes a cascade of neuroinflammatory and pathophysiological events typically resulting in long-lasting physical and cognitive disabilities. The immune response has been described as a 'double-edged sword' as it is important for tissue repair and prevention of invading pathogens early after injury however it can be harmful when prolonged or intensified. It is not known why an estimated 60% of people with a sustained TBI experience moderate to severe long-term disability a year later. Whether the chronic immune response could be responsible for these long-term deficits has not been explored in detail. Hence, we sought to determine the role of the immune system following TBI using the cortical controlled impact model in mice. Mice exhibited a progressive neurological decline over a 32 week period including slow mobility, unilateral movement, uneven gait, tail weakness and spasms. Gait impairment was further confirmed using the DigiGait apparatus which measures changes in motor function and coordination. Interestingly, immunophenotyping using flow cytometry revealed a rapid increase in inflammatory cells and CD4 T-cells within the first week post-TBI, as expected. Remarkably, we discovered that a chronic/adaptive immune response occurs at 8–32 weeks post-TBI. In particular, activated effector cytotoxic CD8 T-cells and activated B-cells were increased in the injured brain at this time period. Surprisingly, a concomitant elevation of circulating antibodies specific to myelin was observed in TBI mice, a typical feature of demyelinating diseases. These results indicate that there is a significant change in immune cell infiltration up to 32 weeks post-TBI coinciding with neurological deterioration. This is consistent with the hypothesis that there is a causal relationship between the cellular immune response and late onset neurodegeneration following brain injury.

Keywords: Neuroimmunology, Neurodegeneration, Inflammation, Traumatic Brain Injury

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C7-10

INCIDENCE OF EARLY FEVER IN TBI VERSUS MAJOR TRAUMA

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Introduction: Up-regulation of aseptic inflammation is a prominent feature of major trauma and may contribute to early fever. Observational studies in traumatic brain injury (TBI) linking fever with poor outcome often lack control groups with major trauma. We hypothesized that patients with TBI would display a higher incidence of early, presumably neurogenic, fever than patients with major trauma (MT) without brain injury.

Methods: We prospectively enrolled patients with MT with and without TBI from a busy level I trauma center ICU. MT was defined as injuries sufficient to warrant ICU admission, without head injury. TBI was defined as admission Glasgow Coma Score (GCS) < 13 not related to intoxication or hemorrhagic shock, or the presence of intracranial hemorrhage on admission CT scan. Severe TBI was defined as GCS 3–8. Hourly temperatures were recorded in both groups for the first 48 hours of hospitalization. Early fever was defined at least one recorded temperature of >38.4°C in the first 48 hours after admission.

Results: Data from the first consecutive 200 subjects of this ongoing trial were analyzed. About half of the cohort met criteria for TBI (n = 99). Injury Severity Score (ISS) was higher in the TBI group (22 [17–29] v. 17 [10–26], P < 0.01). Early fever was equally common between the TBI (16%) and major trauma (16%). When analyzing the group as a whole, controlling for culture verified infection, ISS, Head Abbreviated Injury score (HAIS), the odds of developing early fever was 13% (95% CI 2% to 41%) higher with each point decrease in GCS. Repeating the regression model in only the TBI patients, the odds of developing early fever was 20% (95% CI 2 to 41%) higher with each point decrease in GCS and 75% (95% CI 22% to 92%) higher with each point increase in HAIS.

Conclusion: While the incidence of early fever is similar among critically injured trauma patients, early fever may signify more severe brain injury in TBI. Future work will better characterize the relationship between early fever and aseptic inflammation, which may potentiate secondary brain injury.

Keywords: fever, inflammation, secondary brain injury

C7-11

GREY AND WHITE MATTER PATHOBIOLOGY OF A NEWLY DEVELOPED MODEL OF CHRONIC REPETITIVE CONCUSSIVE HEAD INJURY

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Accumulation of repetitive concussive head injury experienced over the careers of professional athletes in sports, such as, boxing and American football is a major risk factor for the development of neurodegenerative diseases in later life.

We have developed a new mouse model paradigm to explore the risk of repetitive concussive head injury over a prolonged period of time, and the age-associated post-injury factor on neuropathological outcome.

Briefly this new closed head injury model involves delivering two concussive head injuries on a weekly basis, with a minimum inter-injury interval of 48 hours, repeated over 3 to 4 months. Animals were euthanized between 2 to 3 months post last injury.

To characterize and validate our model we have chosen to explore a host of relevant pathological markers. These markers include: different tau species, neurofilament H (NFL-H), α-synuclein, TAR-DNA-binding protein 43 (TDP-43), neuroglial markers (GFAP, IBA-1, CD45, vimentin), inflammatory cytokines (IL-1β, TNFα, IL-6, 1L-4, 1L-10), axonal markers (MBP, APP, Luxol fast blue, silver staining) and lipid species. We correlate these pathological and biochemical profiles with neurobehavioral outcome in tests that examine sensorimotor performance (open field), anxiety (elevated plus maze), social interaction/memory (3-chamber test) and cerebral blood flow (laser Doppler imager). Our data thus far shows a significant dramatic increase in neuroglial markers in injured animals compared with shams. Axonal integrity was significantly altered in injured animals at chronic timepoints post-injury. No significant changes were observed in α-synuclein or TDP-43. A reduction in total tau (tau46) levels was observed in correlation with an apparent increase in tau oligomer level (TOC-1). Other biochemical and behavioral analyses are currently ongoing in this model. This model could be useful in examining chronic effects of repetitive concussion over-life span of individuals involved in sport.

This study is funded by the Roskamp Foundation.

Keywords: hTau mice, repetitive concussions, ageing, biochemical profiles, neurodegeneration

C7-12

COMBINED HEAD INJURY PLUS RADIATION EXPOSURE SHIFTS SYSTEMIC RESPONSE TO IRRADIATION FROM ANTI- TO PRO-INFLAMMATORY

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A subpopulation of victims of a nuclear fission device may sustain both ionizing radiation and traumatic brain injury. Despite advances in the understanding of pathophysiology of whole body irradiation (WBI), little is known about the mechanisms of damage after combined WBI and head injury. Here we developed a combined WBI plus traumatic brain injury model and tested the hypothesis that combined injury will enhance systemic and cerebral inflammatory response vs. either injury alone. Eleven week old C57BL/6NTac male mice were divided into 4 groups: naïve, WBI only (9.1 Gy), controlled cortical impact (CCI) only and combined WBI + CCI. Mice were sacrificed at 24h or 40d after injury. Levels of thirteen cytokines, six chemokines, and three growth factors were measured in serum and in three brain regions (cortex, hippocampus and striatum). 24h serum levels of IL-6, KC, and G-CSF were higher after WBI + CCI vs. either injury alone. Irradiation specifically increased serum IL-10 levels at 24h vs. naïve, CCI and WBI + CCI. By 40 days levels of inflammatory mediators normalized in the serum. The effect of irradiation on the brain was primarily seen in the hippocampus with increases in IL-5, IL-7, IL-15, TNF-α, Rantes and MIP-2 at 24 h. The effects of CCI and WBI + CCI on cerebral inflammatory mediators were similar and observed in all three brain regions tested with robust increases in G-CSF, IL-6, TNF-α, KC, IP-10, MCP-1, Rantes, MIP-1β and MIP-2 at 24 h. Only IP-10 and Rantes remained elevated in striatum at 40d after WBI + CCI while tissue cytokine levels normalized by 40d after WBI or CCI alone. Combined injury enhanced acute systemic pro-inflammatory

response compared to WBI or CCI alone. Sustained increases in IP-10 and Rantes might facilitate recruitment of macrophages/microglia in striatum after combined injury. Defining the mechanisms underlying damage from secondary insults could be vital to development of radiation mitigators.

Support: U19-AI068021, NS061817, NS076511.
Keywords: Multiplex

C7-13

NOCICEPTIVE STIMULATION INDUCES CASPASE 1 ACTIVATION FOLLOWING SPINAL CORD INJURY

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Processes that unfold within the first 48 hours of spinal cord injury (SCI) modulate cell death and determine, to a large extent, long-term prognosis. We have shown that nociceptive signals can influence these processes and the development of secondary damage. Based on studies from a transection model, we hypothesize that nociceptive input after injury undermines cell survival, impairs recovery of locomotor function, and promotes neuropathic pain. However, the mechanism of impaired recovery following nociceptive input is relatively unknown. Here, we used two different models of nociceptive stimulation (uncontrollable electrical stimulation to the tail or intradermal capsaicin injection to a hind paw) to explore the mechanism of impaired recovery following spinal cord injury. We examined locomotor recovery following injury as well as the underlying cellular mechanisms using immunoblotting of the lesion site. Either intradermal capsaicin injection or uncontrollable tail shock significantly impaired locomotor recovery for at least 28 days when given 24 hours after injury. In addition, nociceptive input increased protein expression of active caspase 1 compared to control subjects. Further, subjects receiving capsaicin or shock treatment showed increased processing of the pro-inflammatory cytokines IL-1beta and IL-18. These data suggest that after spinal cord injury, nociceptive stimulation promotes the activation of an inflammasome and leads to caspase 1 activation, inflammatory cytokine processing, and potentially pyroptotic cell death. Future work is examining the cell types responsible for inflammasome activation, other mechanisms of cell death, and potential pharmacologic targets that may reverse this effect. [Supported by Neilson Foundation and Mission Connect grants to JG]
Keywords: pyroptosis, pain, spinal cord injury, inflammation

C7-14

TIBIAL FRACTURE EXACERBATES TRAUMATIC BRAIN INJURY OUTCOMES AND INFLAMMATION IN A MOUSE MODEL OF MULTI-TRAUMA

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Multi-trauma is a common medical problem worldwide, and often involves concurrent traumatic brain injury (TBI) and bone fracture. Despite the high incidence of combined TBI and fracture, pre-clinical TBI research commonly employs independent injury models that fail to incorporate the pathophysiological interactions occurring in multi-trauma. Here we developed a novel mouse model of multi-trauma, and investigated whether bone fracture worsened TBI outcomes. Male mice were assigned into four groups: sham-TBI + sham-fracture (SHAM); sham-TBI + fracture (FX); TBI + sham-fracture (TBI); and TBI + fracture (MULTI). The injury methods included a closed-skull weight-drop TBI model and a closed tibial fracture. After a 35-day recovery, mice underwent behavioral testing and MRI. MULTI mice displayed abnormal behaviors in the open-field compared to all other groups. On MRI MULTI mice had enlarged ventricles and diffusion abnormalities compared to all other groups. These changes occurred in the presence of heightened neuroinflammation in MULTI mice at 24 h and 35 days post-injury, and elevated edema and blood-brain-barrier disruption at 24 h post-injury. Together these findings indicate that tibial fracture worsens TBI outcomes, and that exacerbated neuroinflammation may be an important factor that contributes to these effects, which warrants further investigation.

Keywords: Multi-trauma, Polytrauma, Animal model, Inflammation, MRI, DTI

C7-15

NADPH OXIDASE 4 INHIBITION REVERSES IRON INDUCED PERTURBATIONS OF REACTIVE OXYGEN SPECIES WITHIN ACTIVATED MICROGLIA

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Iron is an essential element for cellular homeostasis. It facilitates molecular rearrangement that aids in ATP creation, myelin synthesis, and a myriad of enzymatic reactions. Recently, iron accumulations within the brain have been associated with pro-inflammatory disease states, such as Parkinson's or Alzheimer's. There are similarities between the inflammatory cascade of these diseases and traumatic brain injury (TBI). Since microglia are the primary mediators of inflammation within the brain parenchyma, we hypothesized that excessive iron can exacerbate the microglia inflammatory response by accentuating activity of NADPH oxidase 4 (NOX4), a known reactive oxygen species (ROS) synthesizer. Utilizing the BV2 microglial cell line, we evaluated the effect of iron sulfate ($FeSO_4$) on microglial related inflammation and NOX4. BV2 cells were cultured with lipopolysaccharide (LPS) prior to addition of $FeSO_4$ for 24 hours prior to evaluation of ROS, cell death, and nitric oxide (NO) release. Iron alone had no effect on any outcome measure in microglia. However, ROS production was significantly elevated by $FeSO_4$ in a dose-dependent manner when cells were pre-stimulated with LPS. Neither $FeSO_4$ nor LPS induced significant changes in cell death. Finally, assessment of NO showed a robust response of the BV2s with LPS treatment ($p < 0.001$), however no difference existed between the LPS exposed group and those groups with $FeSO_4$ and LPS. In order to determine the mechanism of $FeSO_4$ perturbations, we used the NOX4 specific inhibitor, GKT137831. GKT137831 reduced the production of ROS in both LPS and LPS + $FeSO_4$ treated microglia to control levels. These results now show that $FeSO_4$ increases ROS expression in activated microglia, and suggest that iron induced ROS expression in microglia may depend on NOX4 activation. Elevated ROS can play a role in inducing inflammation and neuronal apoptosis; our data now

suggests that both iron and NOX4 are involved in this response and targeting of NOX4 may have therapeutic benefits.

Keywords: Microglia, Inflammation, NOX4, Iron

C7-16

ALTERATIONS OF PROTEASOME DYNAMICS FOLLOWING TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) is a debilitating disorder that can permanently impair brain function leading to long term cognitive, affective and motor deficits. The primary injury often leads to numerous secondary effects including microglia activation, inflammation and disturbances in protein homeostasis. By selectively targeting proteins and peptides for degradation, the ubiquitin-proteasome system (UPS) helps maintain optimal levels of cellular proteins and in so doing mitigates some of the primary and secondary effects of brain injuries. The 26S proteasome is a dynamic enzyme complex that responds to cellular injury by altering the rate of protein degradation and level of antigen presentation. However, the molecular mechanisms controlling these processes remain unclear. We performed controlled cortical impact injury on adult mice to assess proteasome assembly and function. We found increased expression of the immunoproteasome catalytic subunits and interferon gamma (IF-g) in injured mice compared to sham controls indicative of a mounting immune response. Given the role of activated microglia in the CNS immune response, we investigated proteasome dynamics in BV2 microglia cell line following activation with interferon gamma IF-g. Using native gel electrophoresis we found that microglia activation resulted in increased assembly of immunoproteasomes and reduced presence of the constitutive proteasome. Furthermore, the non-catalytic proteasome subunits were unchanged and chaperone proteins responsible for de novo constitutive and immunoproteasome synthesis were unaltered. Our findings suggest that the 26S proteasome is converted to the immunoproteasome following injury by substituting the catalytic subunits in order to facilitate the immune response to trauma.

Keywords: Proteasome, Interferon gamma, microglia

C7-17

MULTIPLE AROMATIZATION MECHANISMS INFLUENCE MORTALITY AND CNS SECONDARY INJURY PROFILES AFTER SEVERE TBI

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Although estradiol (E2) has several neuroprotective qualities, high systemic E2 levels can occur early after severe TBI, despite the uniform occurrence of acute hypogonadotropic hypogonadism, and can contribute to poor outcome. To better understand the production (via aromatization) and complexity of E2 in TBI, we evaluated 1) systemic and CNS contributors to E2 production, 2) E2 associations with 6-month mortality, and 3) CNS E2 associations with CNS s100b, cytochrome-C, and inflammatory load. We studied 187 subjects with severe TBI, aromatase genotypes, and available serum and cerebrospinal fluid (CSF) samples collected over 5d post-injury for hormone and TBI biomarkers. After controlling for covariates, serum biomarkers (E2, estradiol/testosterone (E2:T) ratio, TNFα), and aromatase genetics (rs4646), relevant interactions were modeled to assess 6-month mortality risk. There was a significant interaction between E2:T ratio*rs4646 where CC homozygotes with higher E2:T had reduced mortality risk versus A-carriers ($p = 0.001$). Also, E2 and the E2:T ratio*TNFα interaction tended to be associated with mortality ($p = 0.06$) suggesting unique aromatization mechanisms leading to serum E2 production. Importantly, aromatization mechanisms that contributed to serum E2/T and mortality risk accounted for ~19% of the variance observed with CSF E/T ratios. A separate CSF and genetics mortality prediction model showed rs4646, rs2470152, rs2470152*CSF E2:T ratio interaction influenced mortality, where higher ratios, among those with the rs2470152 risk variant, were protective ($p = 0.018$). Finally, higher covariate adjusted CSF E2/T ratios were associated with lower CSF inflammation, S100b levels, and cytochrome-C levels. Together, these data show 1) multiple mechanisms contribute to aromatization and E2 production after TBI 2) E2 has complex opposing effects on mortality in the periphery vs. CNS, and 3) CNS E2 protective effects are associated with biochemical evidence of a reduction in secondary injury.

Keywords: rehabilomics, aromatization, modeling, mortality, TBI, genetics

C7-18

SERUM TUMOR NECROSIS FACTOR-α ASSOCIATION WITH MORTALITY SIX MONTHS AFTER TBI: MECHANISTIC RELATIONSHIPS WITH ESTRADIOL

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Traumatic Brain Injury (TBI) causes ~1/3 of injury-related deaths yearly in the USA, and there are no approved neuroprotective therapies, justifying continued study of acute pathophysiological contributors to mortality. Tumor necrosis factor-α (TNFα) is a pleiotropic, pro-inflammatory cytokine that is acutely elevated and a primary initiator of the immunological response to TBI. TNFα is also critical for aromatization and adipose tissue production of estradiol (E2), a known mortality marker in TBI. We established how acute serum TNFα measured from samples (collected over the first 5d after TBI) influenced mortality outcomes, using time-to-event analyses in a prospective cohort ($n = 130$). After quartiling TNFα and E2 levels for the cohort, we determined relationships between acute serum TNFα and 1) serum E2 and 2) cerebrospinal fluid (CSF) TNFα, with respect to mortality. Among a subgroup of survivors ($n = 37$), mean sub-acute (weeks 2–12) serum TNFα was explored for relationships to sub-acute E2. After controlling for covariates, there was a 2-fold increase in the hazard of death per quartile increase in acute serum TNFα [HR = 2.00, 95% CI (1.31, 3.08), $p = 0.001$]. Acute serum E2

tended to be associated with time until death ($p = 0.09$), suggesting that TNFα levels account for some E2 variance influencing mortality. Acute serum TNFα and E2 were highly correlated ($r = 0.54$, $p = < 0.001$) among non-survivors, but not among survivors ($r = 0.10$, $p = 0.38$). Sub-acute serum TNFα and E2 were not correlated ($r = -0.08$, $p = 0.64$). Acute serum and CSF TNFα showed a modest correlation ($r = 0.21$, $p = 0.05$), but age-adjusted CSF TNFα levels were not associated with mortality ($p = 0.07$). Acute serum TNFα was associated with E2 and 6-month mortality risk, suggesting possible systemic TNFα mortality effects. Future studies should examine whether acute serum TNFα manipulation might impact acute E2 production and survival post-TBI.

Keywords: rehabilomics, Tumor Necrosis Factor-α, estradiol, serum

C7-19

ANTI-INFLAMMATORY DRUGS SHIFT PROPORTIONS OF ACTIVATED MICROGLIA FOLLOWING EXPERIMENTAL DIFFUSE BRAIN INJURY

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Neuroinflammation contributes to secondary pathology of diffuse traumatic brain injury (TBI). If not tightly controlled, neuroinflammation may modify the function of neuronal circuits. Circuits govern behavior; with alterations to circuits behavioral morbidities can eventuate. We hypothesized that over the counter anti-inflammatory drugs would mitigate neuroinflammation (microglial activation) thus reducing behavioral morbidities following experimental diffuse TBI in rats. To model moderate diffuse TBI, adult male rats were subjected to midline fluid percussion injury. Fifteen minutes post-injury, rats were injected (intraperitonealy) with acetaminophen (40 or 20 mg/kg), aspirin (20 or 10 mg/kg), ibuprofen (60 or 20 mg/kg) or equal volume vehicle. Subsequent injections were given twice daily for one week. Sham rats were not included, as no changes in neuroinflammation occur with surgery. Brains were collected 7 days post-injury (dpi), and immunostained for microglia (Iba-1). Microglial proportions (ramified, activated, rod or amoeboid) were analyzed in the sensory cortex, a region harboring neuropathology. Sensory cortex of vehicle-treated rats had predominantly activated microglia. Acetaminophen and ibuprofen treated rats, showed a shift in the proportion of activated microglia towards ramified morphology in sensory cortex. Whereas, aspirin-treated rats showed a shift in proportion of activated microglia to rod microglia in sensory cortex. To determine the effects of treatment on neuroinflammation and behavior, an additional group of rats were brain-injured and treated with acetaminophen (40 mg/kg), aspirin (20 mg/kg), or vehicle. Treatments were chosen due to effectiveness in shifting microglial proportions without excessive weight loss (noted in ibuprofen groups). Behavioral morbidity was assessed in brain-injured rats via the whisker nuisance task at 28 dpi. Over the counter anti-inflammatory drugs have the capacity to alter neuroinflammation. We suggest that shifts in proportions away from activated microglia will be associated with reduced behavioral morbidities. Partially supported by NIH NINDS R01NS065052 and PCH Mission Support Funds.

Keywords: Microglia, Anti-inflammatory drugs, Behavioral morbidity, Diffuse brain injury

C7-20

P75NTR MEDIATES SYSTEMIC INFLAMMATORY RESPONSES BY MODULATING DIFFERENTIATION OF MYELOID CELLS

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Traumatic brain injury (TBI) leads to pro-inflammatory responses in both CNS and peripheral organs. The inflammatory responses may be involved in the subsequent development of clinical systemic inflammatory response syndrome, which eventually causes immune dysfunction and increases susceptibility to infection in chronic TBI patients.

Previously, we found that blocking the p75NTR signaling pathway by SARA, a selective p75NTR antagonist, inhibits tissue damage and increases functional behavioral outcomes after cortical contusion injury (CCI) TBI in rats. Strikingly, blocking p75NTR signaling reduces microglia activation as well as leukocyte trafficking into the injured brain.

Here, we demonstrated the possible role of p75NTR in peripheral immune cell responses after TBI. Using a CCI-TBI model in C57Bl/6 WT mice, flow cytometric analysis showed that the population of inflammatory monocytes ($CD11b^{+}Ly6C^{high}$) was significantly increased in circulation and the injured brain at 1 week, but downregulated at 6 weeks after TBI. However, the population of mature myeloid cells ($CD45^{high}CD11b^{+}$, $CD45^{high}CD11b^{+}F480^{+}$ and $CD45^{high}CD11b^{+}CD11c^{+}$) was significantly increased and accumulated in the injured brain for 6 weeks after TBI. Interestingly, inflammatory monocytes ($CD11b^{+}Ly6C^{high}$) were accumulated in spleen after TBI. We also demonstrated significantly increased gene expression of pro-inflammatory mediators by qRT-PCR in spleen after TBI. Interestingly, mice treated with daily SARA reduced the number of inflammatory monocytes/macrophages in circulation, the injured brain, and spleen. In addition, SARA treatment results on the inhibition of TBI-induced pro-inflammatory mediators in the spleen. Further, we found that TBI reduces TCR signaling, which was reversed by SARA.

Together, our new findings suggest that p75NTR mediates pro-inflammatory responses by modulating myeloid differentiation in circulation and SARA restores T cell function in spleen, which is critical for immune susceptibility and may contribute to the therapeutic effects of SARA after TBI.

Keywords: p75NTR, traumatic brain injury, systemic inflammation, inflammatory monocytes

C7-21

SIMULTANEOUS EXPRESSION OF M1/M2 MACROPHAGE POLARIZATION PHENOTYPES FOLLOWING TBI

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Focal traumatic brain injury induces a wide array of inflammatory responses principally mediated by cells of the innate immune system, such as microglia and macrophages. Much attention has been paid as of late to categorize the neuroinflammatory response following TBI within the linear constraints of macrophage polarization

phenotypes. *In vitro*, cultured macrophages exposed to specific cytokine cocktails express a relatively predictable gene expression profile that has led to a classification system analogous to T-cell polarization states. Specifically, *in vitro* stimulated macrophages can be classified within activation states termed M1 and M2 (M2a, M2b, M2c) depending upon exposure to a particular cytokine(s). Problematically, this linear classification system has been consistently used to define microglia/macrophage response following brain trauma, such that these responses are viewed as 'either or' or 'on/off'. We have recently shown that TBI induces a milieu of gene expression responses associated with these defined polarization states, which vary across time and importantly overlap such that both M1 and M2 are expressed simultaneously. In the current study we examined TBI-induced expression of M1 and M2 markers using immunofluorescent labeling acutely after injury. Specifically, we show that in the ipsilateral tissue there is simultaneous expression of antigenic markers associated with both M1 and M2 profiles on the same cell. Phenotypic antigen markers of M1 and M2 were CD45, CD68, MARCO, YM1, CD206, and CD36. Co-staining using Iba1 and F4/80 defined these cells as microglia/macrophages. In the context of trauma, the concept of microglia/macrophage polarization is semantically and biologically incorrect due to the Janus-faced nature of these cells.

Keywords: M1, M2, microglia, macrophage, polarization

C7-22

NOX2 REGULATION OF MICROGLIAL ACTIVATION IN THE TBI BRAIN: A NOVEL MECHANISM FOR NEUROPROTECTION AND POST-TRAUMATIC REPAIR

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Microglia can be polarized towards either an M1-like/classical or M2-like/alternative activation status in response to injury. These phenotypes can mediate chronic neuroinflammation or promote tissue repair, respectively. Activation of NADPH oxidase (NOX2/gp91^{phox}) is an important mechanism involved in pro-inflammatory signaling in microglia. We reported that NOX2 is chronically expressed in M1-like microglia in the peri-lesional area 1 year following controlled cortical impact (CCI) in mice. Here we compared wild-type (WT; gp91$^{phox+/+}$) and NOX2-deficient (NOX2-KO; gp91$^{phox-/-}$) mice to investigate the role of NOX2 in posttraumatic microglial polarization.

Three-month old WT or NOX2-KO male mice were subjected to CCI (6 m/sec, 2 mm depth), and cohorts were followed for 1–28 d post-injury. M1-/M2-like polarization was analyzed by qPCR, flow cytometry, Western blot, and immunohistochemistry. Neurogenesis was assessed using doublecortin (DCX) immunohistochemistry; motor recovery and histology were assessed using a beam walk test and stereological methods.

In WT TBI mice, NOX2 was expressed in reactive microglia (CD68+/Clic1+) in peri-lesional cortex through 28d; NOX2-KO significantly reduced CD68/Clic1 expression at 3 and 7d post-injury. Flow cytometry analysis of isolated microglia/macrophages revealed that IL-4Rα and its downstream signaling pathway (STAT6/JAK3) were significantly increased in CD45^{high} microglia/macrophages of NOX2-KO TBI mice compared to WT controls. M2-like polarization (Arg1, Ym1, TGFβ) was increased at 3d post-injury in NOX2-KO, with effects sustained through 21d. There was significant reduction M1-like polarized microglia/macrophages (IL-1β, TNFα, IL-12, iNOS, CD16/32) in NOX2-KO TBI mice. M1/M2-like changes were associated with increased numbers of DCX-positive cells in the subventricular zone, striatum and peri-lesional cortex, indicating increased neurogenesis. NOX2-KO TBI mice also showed significantly improved motor function and reduced cortical neurodegeneration at 21d.

Thus, after TBI NOX2-KO mice exhibit enhanced IL-4Ra-mediated signaling, greater M2-like repolarization, and reduced neurodegeneration. Moreover, altering the M1-/M2-like balance appears to support increased neurogenesis. These data indicate that NOX2 drives the M1-like polarization of microglia/macrophages after TBI, and that inhibiting this pathway limits tissue damage and may promote tissue repair.

Keywords: Microglial phenotypes, NOX2, neurodegeneration, Tissue repair

C7-23

PHOSPHODIESTERASE 4B INHIBITION AS AN ANTI-INFLAMMATORY TREATMENT FOR TRAUMATIC BRAIN INJURY

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The anti-inflammatory effects of phosphodiesterase 4 (PDE4) inhibitors are well established in CNS injury models. Knock out studies have indicated that PDE4B is predominantly responsible for the anti-inflammatory effects of pan-PDE4 inhibition. In the absence of PDE4B, neutrophil infiltration and tumor necrosis factor (TNF) are reduced in models of systemic inflammation. Furthermore, PDE4B2 is upregulated in the injured cortex after traumatic brain injury (TBI). In other models, PDE4B2 is expressed in microglia, macrophages and neutrophils. However, whether PDE4B2 is localized in inflammatory cells after TBI, and whether PDE4B inhibition reduces inflammation and improves histopathological outcome after TBI is unknown. To address this, adult male Sprague Dawley rats received moderate parasagittal fluid-percussion brain injury (2 ± 0.2 atm) or sham surgery. Flow cytometry was used to analyze microglia and infiltrating myeloid-lineage cells isolated from the injured cortex for PDE4B2 expression at 24 hrs after TBI. PDE4B2 was elevated in microglia and infiltrating myeloid-lineage cells at 24 hrs TBI. To determine whether PDE4B inhibition decreases TNF and neutrophil infiltration in the injured cortex, animals received vehicle (5% DMSO in saline) or a PDE4B inhibitor, A33 (2-(4-{[2-(5-chlorothiophen-2-yl)-5-ethyl-6-methylpyrimidin-4-yl]amino}phenyl)acetic acid) at 0.3 mg/kg (i.p.) at 30 min and 5 hrs post-surgery. TNF was measured at 6 hrs post-surgery using an ELISA. Neutrophil infiltration was assessed at 24 hrs post-surgery using flow cytometry. PDE4B inhibition significantly decreased TNF levels and neutrophil infiltration after TBI. To determine whether PDE4B inhibition reduces pathology after TBI, animals received vehicle (5% DMSO in saline) or A33 (0.3 mg/kg, i.p.) at 30 min post-surgery and once daily for 3 days. Cortical contusion was evaluated in serial brain sections stained with hematoxylin and eosin. PDE4B inhibition significantly reduced cortical contusion volume at 3 days post-injury. These results suggest that inhibiting PDE4B after TBI may be a viable treatment to reduce inflammation and pathology. Supported by The Miami Project to Cure Paralysis and NIH/NINDS NS056072 and NS089351.

Keywords: Phosphodiesterase 4B, PDE4B

C7-24

ANTIBODY-MEDIATED AUTOIMMUNITY AFTER CERVICAL SPINAL CORD INJURY: DISTINCT ROLES FOR IGG AND IGM

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Generation of autoantibodies has emerged as an important component in the pathophysiology of spinal cord injury (SCI) and was shown to impair functional recovery in low thoracic SCI models. However, the development of autoantibodies and their role in the outcome of cervical SCI has not been described. The objective of this study was to determine whether autoantibodies of the IgG and IgM class are generated after cervical SCI in a rat model of contusion/compression injury. A C7/T1 clip injury was induced in Wistar rats, whereas sham animals received only a laminectomy. Samples were collected at 2, 10 and 20 weeks post injury. Spinal cords and spleens were stained for IgM and IgG antibodies. Levels of total antibodies in serum were quantified with ELISA. Our results demonstrated increased binding of IgG and IgM in the gracile fasciculus, at 2 weeks post injury. In addition, IgG showed increased binding in the anterior white commissure. Importantly, we detected IgG+ cells that were reminiscent of antibody secreting cells (ASCs), suggesting intraspinal IgG synthesis. Moreover, at 20 weeks, we detected high levels of IgG and IgG+ ASCs in the dorsal horn of injured rats. Despite the chronic presence of IgG in the spinal cord, systemic levels of IgG antibodies and splenic IgG+ASCs declined after injury. Contrary, systemic IgM immunity was pronounced as we detected higher levels of serum IgM and higher IgM+ASCs in the spleen of injured rats. Overall, our data indicate that IgG autoantibodies persist in the spinal cord, whereas IgM antibodies persist peripherally in SCI animals. This work has important implications for our understanding of the key immunological changes after cervical SCI.

Keywords: Spinal cord injury, Autoimmunity, IgM, IgG immunoglobulins

C7-25

EVALUATION OF POLYUNSATURATED FATTY ACID DERIVED MEDIATORS OF INFLAMMATION TO AMELIORATE PRIMARY BLAST WAVE INJURIES IN RATS

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Blast injury is arguably the greatest current threat to Warfighters, and is a leading cause of vision loss from non-penetrating trauma to the eyes or brain, caused by the shock waves. In light of the terrible disability loss of vision presents, there is an urgent need for new drug therapies that can ameliorate neurodegeneration in the eyes (retina) and brain as the result of blast wave exposure. Our hypothesis is that metabolites of polyunsaturated fatty acids, known to be potent pro-resolving mediators of inflammation, i.e., lipoxins, neuroprotectins, and resolvins, will aid as drugs to promote healing of neurons critical to visual function after blast injury. In a rat model of blast wave exposure, we have used electroretinography (ERG), visual discrimination behavior, and histopathology to show, by 14 days post-blast, visual dysfunction occurs along with underlying neurodegeneration of the retinas and brain optic tracts. Blast injury was produced in anesthetized rats that were secured in a compressed air driven shock tube and then exposed to a single blast over pressure wave (20 psi, 8 msec). For therapeutic drug evaluations, rats received one of four compounds, lipoxin A4, protectin DX, resolvin D1, and resolvin E1 (n = 12), which was intravenously administered immediately post-insult and then every other day out to 14 days. Likewise, shams and blasted controls were given saline. Retina and brain status were assessed as found above. Surprisingly, our results suggest these drugs provide slight, if any, neuroprotection towards the blasted rat's visual system. Failure of our approach may be due to ineffective drug delivery to neuronal injury sites from systemic dilution, transient half-lives, and poor penetration of the blood brain retinal barriers. These obstacles might be overcome using tissue targeted drug delivery platforms, e.g., nanoparticles, which if successful will provide an important therapeutic tool for blast injuries.

Keywords: Blast wave, Rat, Eye, Retina, Brain, Polyunsaturated Fatty Acids

C7-26

ACUTE AND SUBACUTE MICRORNA MODULATION FOLLOWING PBBI

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MicroRNAs (miRNAs) are small regulatory RNAs that have recently been exploited as potential biomarkers for several diseases. These RNAs regulate several physiological processes through translational repression or degradation. In this study we investigated novel miRNA changes in our severe penetrating ballistic-like brain injury (PBBI) model. Briefly, this model produces a cavity disrupting 10% of brain volume in injured rats, while a craniotomy is produced in sham controls. Ipsilateral brain tissue and serum were collected (4h, 1d, 3d, 7d) post injury or post sham to examine miRNAs (n = 10 per group). Each animal was run as an independent single array. Our reporting was limited to miRNAs with p value < 0.05 and 1.2 fold (20%) or greater change. At 4h, 4 miRNAs were downregulated and 19 miRNAs were upregulated. At 1d post PBBI 3 miRNAs were attenuated and 4 miRNAs were significantly enhanced. At 3d post injury, 5 miRNAs were decreased and 2 were increased. Seven days post PBBI revealed 9 attenuated miRNAs and surprisingly over 30 were significantly enhanced. Of the miRNAs changed in tissue 8 miRNAs were changed across at least 2 time points including miR-147b, miR-21#, miR- 223, miR-142-3p, miR-142-5p, miR-21, miR-685, miR-34b-5p. These identified miRNAs will be utilized as injury markers in the evaluation of prospective therapeutics. In serum 5 miRNAs were decreased 4h, 6 miRNAs decreased and 1 miRNA increased at 1d, 2 miRNAs decreased and 8 were increased at 3d, and 5 miRNAs were decreased and 2 miRNAs were increased at 7d. Of the altered miRNAs in serum, 1 corresponded with changes in tissue, miR-150. These altered serum miRNAs will be further evaluated for their usefulness as clinically relevant prognostics or theragnostics.

Keywords: microRNA, TBI, Array

C7-27

CCL2 LEVELS IN CSF AND ITS CORRELATION WITH BLAST-INDUCED NEUROTRAUMA IN RATS

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Chemokines and their receptors are of particular interest in the milieu of immune responses elicited in the CNS in response to trauma. The chemokine-mediated accumulation of inflammatory cells in the brain parenchyma is a critical step in the pathogenesis of neuroinflammatory diseases. The neuroinflammatory chemokine ligand 2 (Ccl2) is primarily secreted by blood leukocytes, astrocytes, microglia as well as neurons and has been implicated in the pathogenesis of Alzheimer's disease, brain ischemia and other neurodegenerative diseases. Its role(s) in neurodegeneration and/or neurorestoration after injury remain an area of exploration. Using a rat model of blast-induced traumatic brain injury utilizing an air-driven shock tube, we have investigated the time-course of Ccl2 accumulation in the CSF following single and repeated blast exposures in association with neuro-motor coordination disruptions, inflammatory gene and protein expression changes, and neuropathological changes evoked by these insults. The results reveal that repeated blast exposures caused appreciably greater functional deficits, pathological and biochemical changes compared to a single blast. In addition, acute increases in CSF Ccl2 levels occurred in a severity-dependent manner, suggesting that this response might provide a biological dosimeter following blast exposure. Paralleling its proposed roles in other neurodegenerative disorders, sustained high levels of Ccl2 and increases in its receptor expression in the CNS after blast may contribute to neurodegeneration including chronic traumatic encephalopathy, and therefore should be recognized as a potentially important target for therapeutic intervention.

Keywords: Blast, Neurotrauma, Chemokine, CSF

C7-28

HYPOXEMIA AND HEMORRHAGIC SHOCK DELAY INFLAMMATION AND GFAP-DEGRADATION IN RAT PENETRATING BALLISTIC-LIKE BRAIN INJURY

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Traumatic brain injury (TBI) often occurs in conjunction with additional trauma. Hypoxemia (HX) and hemorrhagic shock (HS) that occurs either alone or in concert with TBI may affect acute inflammatory cytokine production as well as subsequent astrogliosis or protein degradation in brain tissues. This preliminary study sought to quantitate abundance of cytokines and glial fibrillary acidic protein (GFAP) in brain tissues after HS + HX in the rodent model of severe TBI/polytrauma. Interleukin (IL)-1β and macrophage inflammatory protein (MIP)-1α, were measured by ELISA 2h-1day (d) post-injury. GFAP and breakdown product (BDP) quantitation by Western blotting (arbitrary units, AU) was determined 1–7 days post-injury. Statistically significant ($p \leq 0.05$) mean values were determined by 1-or 2-way ANOVA. At 4h post-injury, IL-1β progressively increased and remained elevated in injured groups (0.06 pg/mL in PBBI, 0.07 pg/mL in PBBI + HX + HS). However, 1d after injury only PBBI + HX + HS led to an increase of IL-1β (0.04 pg/mL, vs. Sham and PBBI). The PBBI-mediated rise of MIP-1α 2h (0.27 pg/mL, vs. Sham) was somewhat abrogated in PBBI + HX + HS cohorts (0.14 pg/mL, vs. PBBI). MIP-1α was significantly upregulated in PBBI and PBBI + HX + HS (0.13–0.18 pg/mL, vs. Sham and HX + HS) 4h post-injury. After 1d, PBBI led to an increase (0.28 pg/mL, vs. Sham) was, again, attenuated by PBBI + HX + HS (0.17 pg/mL, vs. PBBI). GFAP and its BDPs were also differentially affected. As expected based on previous studies, total GFAP was vastly increased at 2d (6.2AU, vs. Sham) and remained elevated at 7d (7.5AU, vs. Sham) after PBBI. This increase in total GFAP was less robust in PBBI + HX + HS (3.7AU, vs. Sham). GFAP-BDPs increased 1–2 d after HX + HS alone (0.13AU and 0.40AU, vs. Sham), were most robust 2 days after PBBI (5.9AU, vs. PBBI), but less so in PBBI + HX + HS cohorts (3.3AU, vs. PBBI). Overall, HX + HS delayed early (2h) PBBI-mediated increases in IL-1β and MIP-1α and subsequent (2d) total GFAP or GFAP-BDPs. This data suggests that HX + HS temporarily delays inflammatory processes.

Keywords: Penetrating, Polytrauma, Hypoxemia, Hemorrhagic Shock, Cytokines

C7-29

TEMPORAL AND REGIONAL CHANGES IN MICROGLIAL PROLIFERATION FOLLOWING PENETRATING BALLISTIC-LIKE BRAIN INJURY IN RATS

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Enhanced cellular proliferation that contributes to gliogenesis and neurogenesis occurs after brain trauma. While post-injury neurogenesis stimulates neurorepair, microglial proliferation can cause neuroinflammation that may be detrimental to reparative processes. To design strategies that limit neuroinflammation, we need to understand the temporal course of microgliosis following brain injury. Here we examined the effects of penetrating ballistic-like brain injury (PBBI) on microglial proliferation at various time points (1–14 days) post-injury. Adult rats were subjected to PBBI or sham craniotomy ($n = 5–7$/time-point/group). To capture microglial proliferation, rats were injected with BrdU (50 mg/kg × 3 times at 4h-intervals) prior to different euthanization end points. Iba-1/BrdU/DAPI triple labeling was performed to identify proliferating microglia. In sham rats, microglial proliferation was detected primarily in the dentate gyrus (DG) and sub-ventricular zone. BrdU positive cells were observed throughout the hippocampus, cortex and thalamus in PBBI rats indicating a widespread proliferative response to brain injury. Quantification of proliferating microglia (BrdU/Iba-1) in DG and hippocampus was conducted using a fluorescence microscope equipped with multichannel filter sets. Although sham rats showed some proliferation, only a sparse number of proliferating cells were Iba-1 positive indicating no inflammatory response after sham injury. However, following PBBI, both contralateral and ipsilateral DG and hippocampus showed increased microglial proliferation ($p < 0.05$, compared to sham) at 2 and 3 days that subsided to sham levels at 7 and 14 days post-injury. Although a short sustained burst was observed in microglial proliferation, activated microglia at different activation states (hypertrophied, rod shaped, amoeboid) were present at all the time points studied. Most notably, ''train-like'' rod shaped microglia were observed in brain regions most proximal to the lesion. Overall, our results indicate robust microglial proliferation and activation after

PBBI. Increased microglial activation in neurogenic niches is suggested to dampen the brain's regenerative potential, and our future studies will focus on investigating this effect.

Keywords: Microglia, Proliferation, PBBI

C8 Poster Session VI - Group C: Intracranial Pressure

C8-01

THE EFFECT OF OSMOTIC AGENTS ON CEREBRAL MICROCIRCULATION AFTER TRAUMATIC BRAIN INJURY

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Introduction: Mannitol and hypertonic saline (HTS) are commonly used to treat suspected or documented intracranial hypertension in moderate and severe traumatic brain injury (TBI). The effects of these osmotic agents on altered cerebral blood flow that commonly accompanies TBI is not completely understood. The superiority of one agent over the other is still up for debate. The purposes of this pilot project were to 1) determine whether an intervention to affect cerebral microcirculation could be assessed, 2) assess if mannitol and HTS improve cerebral microcirculation, and 3) assess for a difference in response between mannitol and HTS.

Methods: Adult C57BL mice underwent craniotomy and window placement for *in vivo* two photon imaging of cerebral blood vessels. A fluorescent dye sulforhodamine 101 was injected intraperitoneally to visualize blood vessels and circulating red blood cells (RBC). Moderate TBI was induced using the controlled cortical impact (CCI) method. Mice were randomized to a sham group, a CCI control group, and two treatment groups that received a single intravenous injection of 100 μl of either 20% Mannitol or 3% HTS at 30 minutes post-injury. Cerebral blood vessels in the peri-lesional regions were imaged at baseline, and at 1, 3 and 5 hours post-injury. RBC velocities were calculated based on line-scan and vessel diameters were measured from time lapse images.

Results: CCI caused dramatic decreases in both RBC velocity and cerebral blood vessel diameter. Mannitol and hypertonic saline both significantly increased RBC velocity and the diameters of cerebral arterial, capillaries and veins.

Conclusion: TBI results in abnormal cerebral microcirculation with reduced blood flow in the peri-lesional cortical region. This pilot study shows an intervention's direct effect on blood flow to the injured brain can be assessed, and that both mannitol and HTS improve peri-lesional flow. Further experiments may delineate differences between the two agents, and define a model for testing other potential intervention strategies.

Keywords: Mannitol, Hypertonic Saline, in vivo two-photon imaging, microcirculation

C8-02

RAUMEDIC BOLT: INITIAL CLINICAL EXPERIENCE IN A NEUROSURGICAL POPULATION

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The utility of multi- modality monitoring to provide improved outcomes in neurosurgical patients remains controversial. Regardless, the ability to accurately measure intracranial pressure (ICP) and brain tissue oxygenation can aid the clinician to tailor therapy to each individual's physiology. We provide our initial experience using the Raumedic Neurovent-P with zero-drift technology in a variety of neurosurgical patients.

A retrospective analysis of 39 patients treated under the discretion of the senior author (RAA) from February 2014 through February 2015 was performed. The mean age was 40 (range: 19–65). The average duration of monitoring was five days (range: 3–10 days). The etiology for insertion of Raumedic Neurovent-P intraparenchymal monitor was for traumatic brain injury (n = 37) or aneurysmal subarachnoid hemorrhage (n = 2). Two patients underwent simultaneous external ventricular drainage for concomitant hydrocephalus. Stable patients routinely underwent immediate CT scan for evaluation of monitor placement and potential complications. Antibiotics were maintained until discontination of the monitor.

39 patients underwent single pass successful placement of the Neurovent-P monitor in an anatomically appropriate location. No patients required replacement of the monitor. There were no infections associated with monitor placement. There were 2 hemorrhages associated with monitor placement that did not require further surgical intervention. In several instances, the insertion of the monitor was associated with pneumocephalus which resulted in aberrant brain tissue oxygenation measurements. If the inaccurate recordings did not resolve over 4 hours, the team turned the monitor while in situ to aid in clearing the tip of air or clot to resolve the issue. If it did not resolve, the cables were replaced. Another error occurred when the clinician placing the monitor did not push the catheter through the appropriate final locking mechanism, which led to widely vacillating ICP or pbtO2 numbers. This was resolved by using sterile technique to achieve the final locked position. Insertion and set-up time takes approximately 15 minutes.

The implementation of Raumedic Neurovent-P monitor has allowed for a safe and reliable placement of an intraparenchymal monitor.

Keywords: neuromonitoring, intraparenchymal monitor

C9 Poster Session VI - Group C: Neurotransmitter

C9-01

SEX HORMONE STATUS AND CONTROLLED CORTICAL IMPACT AFFECT DOPAMINE NEUROTRANSMISSION AND RESPONSE TO METHYLPHENIDATE ADMINISTRATION

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Dopaminergic (DAergic) agents are a mainstay of treating cognitive and behavioral impairments following traumatic brain injury (TBI), but little is known about how to personalize these treatments for individuals. Sex hormones alter DA neurotransmission and the responses to DAergic agents. We investigated how sex, hormone status and TBI affects DA neurotransmission and the physiological responses to the clinically utilized DA transporter (DAT) inhibitor methylphenidate (MPH) using fast-scan cyclic voltammetry (FSCV). We used 43 Sprague Dawley rats, separated into male, female, and ovarectomized (OVX) groups that were either naïve or injured using a severe controlled cortical impact (CCI) over the right parietal lobe (4 m/s, 2.9 mm deformation). We examined FSCV DA response amplitudes, and kinetic measures of DA release and maximal clearance rate (Vmax) that relates to local functional DAT density. MPH

enhanced stimulated response amplitudes in all rats, while CCI significantly attenuated these effects in males, females, but not in OVX rats (% attenuation: 104%, $p < 0.05$; 80%, $p < 0.05$; and 26%, $p = 0.48$, respectively). DA release rates were similar between all groups. Vmax was similar between naïve males and females, but was relatively decreased in OVX rats (naïve female vs. OVX: 54.0 ± 3.8 vs. 38.7 ± 5.3 μM/s, $p < 0.05$). Vmax was decreased in male and female rats 2 wks post-CCI (naïve vs. CCI: 51.80 ± 2.4 vs. 40.68 ± 2.2 μM/s, $p < 0.005$), but again, not in OVX rats ($p = 0.72$). After initial reductions in Vmax following MPH in all groups, there were notable sex-based differences in the temporal regulation of Vmax; female and OVX rats had a progressively decreasing Vmax, while male rats, regardless of injury status, had a progressive increase in Vmax to restore reuptake kinetics over the sampling window. These findings demonstrate that CCI and hormonal manipulation alter DA neurotransmission kinetics, and that there may be a need to tailor clinical MPH therapy in relation to sex and hormone status.

Keywords: Rehabilomics, TBI, Dopamine, Gender, Neurotransmission, DAergic

C9-02

DOPAMINE SYSTEM GENETICS AND SEX INTERACT TO AFFECT COGNITIVE DYSFUNCTION AFTER TBI

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There is evidence that genetic variation within dopamine (DA) systems has a sex-specific relationship to cognitive function in healthy populations. TBI results in a hypo-dopaminergic state, thus, DA genetic variation may prove important in understanding cognitive heterogeneity in TBI populations. We assessed sex and genetic variability at 4 loci within three DA genes in 99 Caucasian adults ($n = 18$ women; $n = 81$ men) with moderate/severe TBI on cognitive outcomes. We used normed data from eight neuropsychological tests to measure cognitive impairment. Four cognitive domain scores capturing information about memory, attention, language fluency, and executive function were used to generate an overall cognitive composite score. We then created a Gene Risk Score (GRS) using the following polymorphisms: *COMT* Val158Met, *ANKK1* Taq1A, *DRD2* rs6279, and *VMAT* rs363226. These variants were selected based on previous association with cognition and their coverage of DA systems. GRS was created by analyzing mean differences between sexes for each variant and assigning risk values based on their significance with respect to overall composite scores at both 6 and 12 months. GRS was significantly associated with overall cognitive composite score at 6 months ($r = -0.27$, $p = 0.011$), with a trend for significance at 12 months ($r = -0.20$, $p = 0.111$) post-injury. When adjusting for age, sex, injury severity, and education, GRS was a significant predictor of cognition 6 months ($p = 0.0017$, model $r^2 = 0.277$) and 12 months ($p = 0.0096$, model $r^2 = 0.313$) post-TBI, with the GRS capturing 0.076 and 0.095 of each model's variance (r2) respectively. GRS approaches reflect multiple sources of biological variation that provide important contributions to complex signaling pathways such as DA systems with cognition. These results suggest the potential importance of both sex and DA genetics when assessing and managing cognitive dysfunction post-TBI.

Keywords: sex-specific, gender, dopamine, genetics, cognitive recovery, rehabilomics

C9-03

ADMINISTRATION OF LITHIUM IMPROVES NEUROTRANSMISSION AND INCREASES VESICULAR DOCKING PROTEINS IN THE STRIATUM AFTER CCI

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Traumatic brain injury (TBI) impairs neuronal function and can culminate in lasting cognitive impairment. While impaired striatal dopamine release is reported after experimental TBI, little is known about the mechanisms underlying this consequence. Our previous work suggests that reductions in proteins comprising the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex, the machinery facilitating vesicular fusion, may contribute to altered synaptic vesicle properties and impaired neurotransmission. Cysteine-string protein α (CSPα) is an important chaperone protein that facilitates SNARE complex formation and is increased in response to lithium treatment. The objective of this study was to evaluate the effect of lithium administration on CSPα abundance and neurotransmission in the striatum after controlled cortical impact (CCI).

Methods: Sprague-Dawley rats received CCI (2.7 mm) or sham injury. Animals were treated with vehicle or 1.0 mmol/kg/ml lithium chloride daily (i.p. injection) for 1 wk, beginning 5 minutes post-injury. The brains were dissected at 1 wk post-injury and processed for immunoblotting of CSPα ($n = 3$–4/group). At 1 wk post-injury, CCI-injured and sham-injured rats were subjected to microdialysis and evoked dopamine release was measured by high-performance liquid chromatography ($n = 4$–5/group).

Results: CCI results in a 40% reduction in CSPα abundance in the striatum following injury. Treatment with lithium after CCI increased CSPα in the striatum by 15%, compared to vehicle treatment. CCI was associated with a significant reduction in peak dopamine release following high-potassium stimulated release ($p < 0.05$). The peak dopamine levels with post-traumatic treatment of lithium were not different from sham injury ($p = 0.75$).

Conclusions: These findings provide the first evidence of altered SNARE protein abundance in the striatum after CCI. We demonstrate for the first time that lithium improves neurotransmission following TBI. These findings suggest that treatment with lithium after TBI may increase the abundance of important proteins that facilitate neurotransmitter release into the synaptic cleft.

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Keywords: Synapse, neurotransmission, vesicle, CCI

C9-04

TRAUMATIC BRAIN INJURY PRECEDES ENHANCED FEAR CONDITIONING AND SUBREGIONAL CHANGES IN HIPPOCAMPAL EXCITATORY/INHIBITORY TONE

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Individuals with mild traumatic brain injury (mTBI) often develop affective changes such as anxiety, depression, or symptoms resembling posttraumatic stress disorder (PTSD). It is not clear how mTBI induces PTSD-like symptoms, although studies show activation changes in brain regions involved in fear learning; such as prefrontal cortex (PFC), amygdala (AMY), and hippocampus (HC); with dorsal (dHC) and ventral (vHC) demonstrating subregion-specific responses. Here, we used a mouse model of mTBI to examine effects of injury on fear behaviors and associated neurochemical alterations.

Anesthetized male C57BL/6 mice (10–12 wk) given a mild, midline impact over intact skull, sham surgery, or no surgery (naïve) were assessed for fear response (freezing) to contextual fear conditioning (FC) at 14 d post-injury, using a 5-phase paradigm (habituation, acquisition, extinction, reinstatement, reinstatement recall). Brains were harvested for proton magnetic resonance spectroscopy (^{1}H-MRS) analysis *ex vivo* at 25 d post-injury for excitatory/inhibitory neurochemical assessment.

mTBI mice demonstrated increased freezing during acquisition and extinction, compared to controls (combined naïve/sham). No differences in freezing emerged between groups at baseline or reinstatement; but mTBI mice showed more freezing during reinstatement recall, compared to controls. At 25 d post-injury, HC exhibited subregion-specific neurochemical profiles: decreased dHC GABA and increased vHC glutamate in mTBI compared to controls. PFC and AMYG did not differ neurochemically between mTBI and controls.

Changes observed in conditioned fear in mTBI mice resemble FC reported in PTSD and observed clinically in mTBI. Decreased dHC GABA may reflect reduced inhibitory neurotransmission, with increased vHC glutamate reflecting greater excitatory neurotransmission. These data suggest increased excitatory tone in both regions, achieved through different mechanisms. This model of mTBI-induced alterations in FC may give insight into regionally distinct HC influence on the development of affective disorders following mTBI.

Keywords: Mild TBI, Fear Conditioning, Magnetic Resonance Spectroscopy, GABA/Glutamate, Mouse Model, Hippocampus

D1 Poster Session VII - Group D: Bioengineering

D1-01

SUBCONCUSSIVE HEAD IMPACT HISTORY FOR CONCUSSED AND NON-CONCUSSED COLLEGE FOOTBALL PLAYERS

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Head impact history has become a significant clinical factor for concussion, with studies reporting more problematic outcomes for athletes that sustained 3+ concussions. Experimental studies report decreased biomechanical tolerance for animals that sustained prior concussions. It can be hypothesized that subconcussive head impact history influences concussion risk in humans. The current objective was to outline differences in subconcussive impact history between concussed and non-concussed athletes. Division III college football players were consented and enrolled for the 2013 season. Head impact metrics were collected for games and contact practices using xPatch acceleration sensors (X2 Biosystems, Seattle, WA). Impact data were collected for 185 non-concussed and 11 concussed players. Data were divided between 4 position groups (number concussed): offensive line (1), offensive backs (3), defensive line (4), and defensive backs (3). Concussive impacts had a median linear acceleration of 77 g. The number of subconcussive impacts above 25% of the median concussive acceleration was compared between concussed and non-concussed groups. Analysis was divided between games and practices and normalized by number of games/practices per player. For concussed players, impacts before the injury dates were analyzed. Overall, 35% more subconcussive impacts were sustained during games than practices. Concussed defensive players had 103% more subconcussive impacts than non-concussed defensive players during games (+133% for backs, +73% for linemen). This trend was not evident for defensive players during practices or offensive players during games or practices. Although the trend for pre-injury subconcussive exposure for concussed defensive players is intriguing, these data in general do not support the hypothesis that subconcussive head impact history contributes to greater concussion risk. However, this study included a limited dataset and significant trends may emerge with larger sample sizes. Nonetheless, this forms the basis for ongoing investigation into effects of subconcussive impact history on risk and biomechanics of athlete concussion.

Keywords: head acceleration, traumatic brain injury, biomechanics

D1-02

SEX-BASED BEHAVIORAL DIFFERENCES IN RATS FOLLOWING HEAD ROTATIONAL ACCELERATION INJURY

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Literature-supported evidence highlights sex-based differences in traumatic brain injury (TBI) outcomes (clinical and pathological) between males and females. Animal models can quantify these differences in a controlled laboratory environment using identical injury exposures and assessments focused on specific outcomes. This study exposed anesthetized male and female Sprague-Dawley rats to head rotational acceleration or sham procedure. Acceleration magnitude and duration were identical between male and female rats (363 krad/s^2, 3.4 msec). Control rats were exposed to a sham procedure that was identical to the injury protocol without head rotational acceleration. Behavioral assessments conducted during the first week following injury included Morris Water Maze (MWM) and Elevated Plus Maze (EPM). Unconsciousness time immediately following injury was not significantly different, although male rats had 22% shorter unconsciousness times. Female rats demonstrated greater post-injury activity, with significantly increased number of EPM arm changes ($p < 0.05$) for injured female rats compared to injured male rats. Compared to sex-matched controls, injured females had 113% increased whereas males had only 20% increased number of arm changes. Male rats demonstrated altered emotionality following injury, with 25% more time in the EPM open areas per entry compared to controls. Injured female rats spent the same amount of time in the open areas of the EPM per entry as controls. Compared to sex-matched controls, injured male rats demonstrated significantly increased MWM unsuccessful trials ($p < 0.05$, +142%), along with greater latency to find the hidden platform during the first (+28%) and

second (+33%) sets of a three-set MWM protocol. MWM behavior of injured female rats was not significantly different from female control rats. This study demonstrated some significant sex-based differences in the magnitude and type of behavioral changes following rotational acceleration TBI across multiple assessments characterizing post-injury activity, emotionality, and cognitive deficits.

Keywords: angular acceleration, gender

D1-03

CREATING A KNOWLEDGE NETWORK FOR TBI RESEARCH: THE ONE MIND PORTAL

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In 2011, the Institute of Medicine published a report entitled ''Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease''. The knowledge network was envisioned as a dynamic system for compiling, integrating and analyzing multiple types of clinical and research data to discover cause and effect relationships on disease outcomes. The traumatic brain injury (TBI) research community has many of the foundational pieces needed for a knowledge network, including common data elements, the Federal Interagency TBI Research Informatics System (FITBIR), the Therapeutic Endpoints Development (TED) project, and numerous clinical studies to collect high quality data. The objective of the One Mind Portal is to connect these existing resources, as well as to add missing components, to enable a user-friendly and effective TBI research knowledge network. A key component in supporting these collaborations is the Portal's digital marketplace. The marketplace is the gateway through which research data — for all brain diseases and injuries — can be accessed from around the globe to foster open-science approaches and scale research in a dramatic way. In addition to allowing researchers to publish their data as packages that can then be downloaded by the research community, the marketplace also features integrated open analysis tools, such as tranSMART and RStudio, for working with complex data. Through the use of open source tools such as tranSMART, curated clinical and outcomes data, neuroimaging and molecular measures can be integrated to provide a community-driven analytics platform for collaborative, translational biomedical research. In conclusion, the first iteration of the One Mind Portal aimed at connecting data, analytical tools, and investigators for the purpose of accelerating TBI research has been created. Future iterations will include advances in technology and resources, and most importantly, be based on user input about what is needed for a productive, collaborative research workspace.

Keywords: bioinformatics, data science, analytics

D1-04

EXPLORING THE LINKS BETWEEN BLAST-INDUCED TRAUMATIC BRAIN INJURIES AND PSYCHOSOCIAL DEFICITS IN RATS

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The aim of this investigation was to explore physical and biological mechanisms linking blast-induced traumatic brain injury (bTBI) to delayed development of post-blast neuropsychiatric abnormalities. Rats were exposed to mild bTBI and evaluated in numerous behavioral metrics including rotor rod (RR), open field (OF), novel object recognition (NOR), social interaction (SI), and social recognition (SR) under normal and anxiogenic conditions. Post-mortem brain tissue was assessed via immunohistochemistry (IHC) and immunoblotting for morphological and biochemical changes in acrolein levels and neuroinflammation. Daily post-injury urine samples were analyzed for changes in acrolein levels. In addition, wireless deformation sensors were implanted to measure brain deformation *in vivo* during blast exposure. Mild blast-exposed rats experienced pronounced psychosocial safety learning deficits (consistently reduced SI time) from 7–12 days post-injury despite a lack of other motor or cognitive deficits (RR, OF, NOR, and SR unchanged). These deficits correlated with 24 hr post-injury elevations of a toxic post-trauma neurotoxin, acrolein, which was elevated up to three days in urine and five days in brain tissue. IHC revealed blood-brain-barrier and microglial inflammatory activity in and around brain regions suspected to mediate normal psychosocial safety learning, where significant brain deformation was also measured *in vivo* at the time of injury. Taken together, bTBI can physically disrupt and biochemically dysregulate the brain in the acute term post injury. Left unabated, these disruptions can lead to neuropsychiatric abnormalities with significant implications for reduced quality of life. Further study in rats may bring critical insight to the analogous struggles of veteran societal reintegration post-combat. Improved protective technology paired with methods for early diagnostic and therapeutic intervention may provide effective mitigation of long-term post-bTBI neuropsychiatric sequelae.

Keywords: TBI, behavior, acrolein, deformation

D2 Poster Session VII - Group D: Modeling

D2-01

MILD TRAUMATIC BRAIN INJURY IN MALE AND FEMALE RATS: CHARACTERIZATION OF A NEW INJURY PARADIGM

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Objective: Mild traumatic brain injuries (mTBI) have significantly increased in the last decade and there is mounting evidence of their adverse cognitive and emotional effects. These effects and the underlying pathophysiology are studied using rodent models, however, in many, force is applied through projectiles or blasts to a stationary animal. These may not adequately induce acceleration and rotation of the animal's head, as is common in human sports-related injuries. Thus, to more accurately reproduce these important features of the injury, we designed a new method for inducing mTBI in rats that includes acceleration of the animal toward a stationary impact zone to produce rapid rotational movement of the head. The present experiment aimed to validate this novel injury model.

Method: Male and female rats sustained mTBI or served as sham-injured controls. Behavioral markers of recovery immediately after injury and activity and memory in the week following injury were collected.

Results: mTBI produced behavioral deficits in males and females. In females, mTBI induced prolonged ataxia in the minutes following injury, increased activity levels four days post-injury, but led to only

mild non-significant deficits in learning the location of a platform in a water maze. In contrast, male mTBI rats did not differ significantly from shams during recovery but displayed marked deficits during spatial learning. A memory retention test conducted a week after spatial learning revealed deficits in both male and female mTBI rats.

Conclusion: These findings confirm the validity of this novel model at the behavioral level and research on adverse neural outcomes is underway; preliminary data indicate that mTBI may reduce hippocampal plasticity. This research has the potential to facilitate a new way to study mTBI and may better complement research on sports-related concussion in humans.

Keywords: Hippocampus, mTBI, Behavior, Injury

D2-02

CLOSED-HEAD SINGLE AND REPEAT CONTROLLED CORTICAL IMPACT IN THE ADULT RAT: EFFECTS ON BEHAVIOR, PHYSIOLOGY, AND PATHOLOGY

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Recently, cases of multiple concussions in athletes have received increased attention. Compared to single concussions (sTBI), repeat concussions (rTBI) can produce significant long-term consequences and increased risk for neurodegenerative disease. However, mechanisms underlying this difference are poorly understood. We developed a clinically relevant closed-head injury model of concussion in the adult rat using a Leica Controlled Cortical Impact (CCI) device. Rats were placed in a stereotax without ear-bars, on a foam-bed base. The head was stabilized against a Plexiglas frame to control impact while allowing head movement. A 6.5 m/s impact was delivered onto the head surface over the sensorimotor-cortex at a depth of 10.0 mm from the skin. rTBI animals received three injuries, 48h apart. At 5–7 days post-injury, rats were assessed using tests of memory (Novel Object Recognition), forelimb coordination (foot fault) and activity/anxiety (open field). Blood corticosterone levels were measured pre-injury and pre-sacrifice (day 8). Results indicate that both sTBI and rTBI animals show deficits in coordination and hypo-locomotion. sTBI rats showed no anxiety but rTBI rats showed a trend towards less time spent in the center of an open field. sTBI rats displayed memory deficits 3d but not 7d post-injury while rTBI rats still showed memory deficits at 7d. Both had higher resting corticosterone levels post-injury. No obvious gross pathology was observed on the cortical surface or in coronal sections. Our data presents a model of closed-head CCI in an adult rat that results in clinically relevant markers of concussion and a delineation between sTBI and rTBI.

Keywords: memory, concussion, motor, anxiety, repeat concussion

D2-03

A COMPUTATIONAL MODEL OF CORTICAL NETWORK FOR QUANTIFYING NEUROBEHAVIORAL SEQUELAE OF CONCUSSION LINKED TO TRAUMATIC AXONAL INJURY

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Background: Mild traumatic brain injury (mTBI) often results in neurobehavioral alterations such as impaired attention, increased reaction time, and deficits in working memory. Diffusion imaging, post mortem studies, and animal models suggest that mTBI primarily affects myelinated axons in white matter tracts. We sought to quantify the neurobehavioral manifestations of concussive mTBI that are linked to traumatic injury of myelinated axons.

Methods: A large-scale biophysically plausible model of cortical tissue was created for studies of neurobehavioral manifestations of traumatic axonal injury. The network was composed of 5120 pyramidal neurons and 1280 inhibitory neurons, communicating via glutamatergic and GABAergic synapses. Importantly, the model architecture reflected intra- and inter- hemispheric cortical organization, including the distribution of non-myelinated and myelinated (callosal) axons and axonal conduction delays. Injury was applied to model corpus callosum axons for quantifying the resulting alterations in cortical dynamics.

Results: The intact model exhibited collective oscillations in the alpha band (8–12 Hz) that are routinely observed in resting non-attending human subjects. Callosal injury induced several clinically observable changes, including injury dose dependent increases in: 1) theta-to-alpha spectral power, as observed in qEEG studies, 2) reduced response to attention-like stimulation, and 3) increased population response time, similar to increased reaction time as observed in neurobehavioral tests on mTBI subjects.

Conclusions: The model results were in a good semi-quantitative agreement with the existing experimental data. This effort is part of a larger goal to link a series of models together in an end-to-end fashion to identify a neurologically based mechanism of concussion and its implication regarding the prognosis and diagnosis of concussion. Computational models of white matter biomechanical response and neurological changes have been developed and are used in conjunction with the present model to complete the linkage of external loading conditions to neurological outcomes. The present model can be used as a platform for modeling neurobehavioral sequelae of mTBI and for linking the observed outcomes to specific injury scenarios.

Keywords: cortical network, neurobehavioral sequelae, reaction time, qEEG

D2-04

VISUAL DYSFUNCTION SCREENING IN MICE AFTER TBI USING AN OPTOMOTOR ASSESSMENT OF THE OPTOKINETIC RESPONSE

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Introduction: Our mouse model of repetitive mild TBI (r-mTBI) produces chronic optic nerve pathology and retinal degeneration. In order to assess the visual function of the mice, we have optimized a mechanical optomotor assay to assess the optokinetic response.

Methods: The optomotor apparatus consisted of a rotating drum containing black and white stripes at varying angular resolutions. Mice were acclimated to the apparatus for a period of 5 minutes in phototopic lighting. Optomotor testing at each resolution consisted of pairs of 2 minute trials with 1 trial in a clockwise rotation followed by 1 trial in a counter-clockwise rotation with an inter-trial time of 30 seconds. Following the completion of the first pair of trials in photopic conditions, lighting was dimmed to scotopic

conditions and the mice were allowed to acclimate for a period of 5 minutes followed by another pair of trials. After the completion of all 4 trials the mouse was returned to the home cage and the next mouse was tested. On subsequent days this testing was repeated with the rotation of the drum increased in a range from 2 to 5 rpm. All trials were recorded with Noldus Ethovision XT.

Results: Optomotor testing and optimization revealed a non-random, quantifiable optokinetic response of the mice which was found by excluding the portions of the trial where the mouse was in motion and by quantifying the angular rate of rotation of the head of each mouse.

Conclusions: By varying the resolution of the stripes we were able to increase the difficulty of the task and determine the optimal conditions for eliciting an optokinetic response in healthy mice capable of discriminating subtle vision deficits. Varying the rotation rate of the optomotor drum also allowed us to determine the optimal speed for eliciting the optokinetic response. The optimized assay will allow us to accurately assess the functional outcome of potential therapeutics for the treatment of TBI-induced visual dysfunction.

Keywords: Optokinetic, Neurobehavior, Optomotor, Animal model, Vision

D2-05

INJURY PROFILES, DEMOGRAPHY AND REPRESENTATIVENESS OF PATIENTS WITH TBI ATTENDING A REGIONAL EMERGENCY DEPARTMENT

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Introduction: A common cause for conflicting results in studies with TBI is the variability in study populations. Several large current international efforts try to recruit unselected samples of patients with TBI attending the participating hospitals. We describe our results and experiences from the prospective recruitment during the TBIcare study.

Methods: TBIcare was an international effort to develop diagnostic modelling for TBI. During the study we aimed at recruiting 200 largely unselected adult patients attending the regional emergency department of the Turku University Hospital, Finland. Exclusion criteria were age <18 yrs, severe pre-injury disability, blast/penetrating injury, more than 2 weeks from the injury, not living in the district, not speaking native language, and uncertain diagnosis of TBI. To be included a need for acute head CT (NICE-criteria) was required.

Results: Of the 632 potentially eligible patients with TBI or suspected TBI during the study we recruited 203 patients. From those who were left out, 53% were because of predefined exclusion criteria and 47% due to logistic/communication reasons. Age <18 yrs (20%), uncertain TBI diagnosis (17%), and not living in the area (14%) were most common groups of exclusion. Lack of information for the research group before discharge was the most common cause for being left out (45%). The final study group had more men that the total eligible population ($p = 0.008$) but no other differences in demographics or injury mechanisms were found.

Conclusions: A lack of prospective 24/7 recruitment by the researchers may easily leave out a significant number of the patients and cause unpredictable bias in the representativeness of the sample. Uncertainty about the diagnosis of TBI is common.

Keywords: traumatic brain injury, demographics, representativeness

D2-06

ANALYZING CONCUSSION SCORE CRITERIA FOR VINYL NITRILE FOAM AND MICROLATTICE MATERIAL USING A ONE-DIMENSIONAL MODEL

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Biomechanics of sports concussions is an important topic of research in the modeling community. In football, lower concussion probabilities are associated with decreased accelerations experienced by the brain after an impact. Studies using Head Impact Telemetry System (HITS) and the Hybrid III System (HIII) have calculated head injury criterion (HIC) and severity index (SI) scores, which have been used to estimate risk for concussion. To develop a rapid throughput system for evaluation of different helmet material properties, we opted for a simple 1D model that includes the helmet shell, padding, skull, and brain with springs and dashpots between components, similar to that developed by [1]. Solving the multiple degree-of-freedom (DOF) mass-damper-spring differential equations can compute the acceleration curves following a blunt impact. We evaluate the HIC and SI scores using this methodology on the vinyl nitrile (VN) foam used widely in sports helmets and compare them with a microlattice (ML) padding developed by Architected Materials and UCLA. The ML load-deflection curves show a 22% decrease in peak force for the same energy absorption when compared with VN foam. The unique structure of the ML leads to increased energy absorption and damping coefficients under hysteresis tests and are related to decreased HIC and SI scores with minor changes in peak brain accelerations(C = 100Ns/m HIC = 154 PeakAcc = 108 m/s^2, C = 1000Ns/m HIC = 67 PeakAcc = 110m/s^2). A 1D-model with parameters fit from experimental padding data can help drive helmet padding designs to lower the probability of sports concussions.

Support: NFL-GE; UCLA Steve Tisch BrainSPORT program, Joseph Drown Foundation

[1]Honarmandi and Sadegh. ''Modeling and Impact Analysis of Football Helmets: Toward Mitigating mTBI.'' *ASME 2012*

Keywords: Modeling, Bioengineering, Concussion

D2-07

A SINGLE CONCUSSIVE BRAIN INJURY TRANSIENTLY DISRUPTS HOME CAGE ACTIVITIES IN MALE AND FEMALE C57BL/6J MICE

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A single concussive brain injury (CBI) can result in prolonged neurological deficits in clinical populations, but functional impairments following a single CBI are often difficult to detect in rodent models using traditional behavioral tests, even in the acute time period following the injury. In this experiment, we employed Any-Maze cages (Stoelting, Co.) to continuously monitor home cage activity, wheel running and ingestive behaviors following CBI. Male and age-matched, cycling female C57BL/6J mice were subjected to a closed-skull concussive brain injury (CBI) delivered via a Leica ImpactOne controlled cortical impact device. Following recovery of the righting reflex, mice were placed into Any-Maze cages, where they remained for three days, followed by testing in an open field and on the y-maze test of spontaneous alternation behavior (working memory). The duration of apnea following CBI was longer in female mice than in male mice. The amount of time to appearance of the righting reflex was also longer in female mice, but there did not appear to be a relationship between duration of apnea and righting reflex recovery. CBI greatly reduced activity in the home cages during the 24 hours following the injury, as measured by decreased movement around the cage, decreased wheel running, and a large reduction in food and water intake. These measures returned to the levels of sham controls within 48 hours following the injury. Injured animals had normal behavior in an open field and unimpaired working memory performance in the y-maze spontaneous alternation test three days following CBI. These results suggest that an identical injury has greater immediate effects on smaller female mice as assessed by duration of apnea and recovery of the righting reflex, but changes in motivated behaviors are equally impaired in both sexes and are resolved quickly.

Keywords: behavior, concussion, ingestion, circadian activity

D2-08

LOCALIZATION OF THE CORTICOSPINAL TRACT IN PIGS: IMPLICATIONS FOR MODELLING TRAUMATIC SPINAL CORD INJURY

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Background: Spinal cord injury (SCI) researchers have predominately utilized rodents for SCI modeling and experimentation. Unfortunately, the large number of developed novel treatments for SCI using rodent models have failed to demonstrate efficacy in human clinical trials. Recently, porcine models of SCI have been identified as a valuable intermediary model for preclinical evaluation of promising therapies to aid clinical translation. However, the localization of the major spinal tracts in pigs has not yet been described. Determining the similarity of the location of the corticospinal tract in pigs compared to humans may therefore provide important evidence for the use of pigs as a vital pre-clinical model.

Objective: We aim to investigate the localization of the corticospinal tract within the porcine spinal cord and determine the similarity to human and rodent anatomy.

Methods: Mature female domestic pigs (n = 4, 60 kg) received microinjections of fluorescent dextran tracers (Alexa Fluor, 10,000 MW, Life Sciences) into the primary motor cortex guided by a STEALTH navigation stereotactic system. At 4 weeks post-tracer injection animals were euthanized, the entire neuroaxis harvested and processed for histological examination. Serial sections of the brain and spinal cord were prepared, imaged and digitally reconstructed to give a 3D visualization of the corticospinal tract location.

Results: The corticospinal tract of pigs is located in the lateral white matter, demonstrating greater similarity to human anatomical structure than that of rodents.

Conclusion: The corticospinal tract in pigs demonstrates anatomical similarity to human, suggesting that the porcine model has importance as a translational intermediary pre-clinical model.

Supported by: UAB Department of Physical Medicine and Rehabilitation

Keywords: Spinal Cord, Tract Tracing, Porcine Model, Corticospinal Tract

D2-09

BIOMECHANICAL AND FUNCTIONAL CHARACTERIZATION OF CHIMERA IN AN APP/PS1 MODEL OF ALZHEIMER'S DISEASE

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Background: In addition to being a leading cause of disability in young people, traumatic brain injury (TBI) is a risk factor for dementia, including Alzheimer's disease (AD). Notably, both amyloid and tau neuropathology can develop after TBI. We recently developed a novel rodent TBI model called CHIMERA (Closed-Head Impact Model of Engineered Rotational Acceleration) that uses a non-surgical procedure to precisely deliver defined impacts to an intact head with unrestrained and reliable head movement. In C57Bl/6, CHIMERA induces significant behavioral deficits, white matter inflammation, axonal damage, and endogenous tau phosphorylation. Here we apply CHIMERA TBI to the APP/PS1 model of AD.

Objective: To characterize acute biomechanical, behavioral, and neuropathological outcomes of repetitive TBI using CHIMERA in APP/PS1 mice.

Methods: CHIMERA was used to induce two mild TBIs (0.5 J impact energy), spaced 24 hours apart in 5-mo male APP/PS1 mice. Head kinematics were assessed using high-speed videography (5000 fps). Acute behavioral, histological, and biochemical outcomes tests were conducted up to 48h post-injury.

Results and Discussion: Head kinematic analysis showed peak displacement of 41.8 ± 3.7 mm, peak angular deflection of 2.3 ± 0.4 rad, peak linear and angular velocities of 5.2 ± 0.4 m/s and 314.0 ± 169.6 rad/s, respectively, and peak linear and angular accelerations of $238.3 \pm 79.2\ g$ and 280.3 ± 168.5 krad/s^2, respectively. Immediately post-TBI, APP/PS1 mice experienced a prolonged loss of righting reflex compared to sham-operated APP/PS1. Behavioral analysis at 48h revealed increased neurological deficits (neurological severity score), and poorer motor coordination (Rotarod) in injured

versus sham APP/PS1. Histological analysis at 48h revealed increased 6E10+ve A-beta deposits, microglial activation (Iba-1), argyrophilic fibre (silver staining), and axonal bulb-like structures (phosphoneurofilaments) in injured versus sham APP/PS1. Together, these results support the hypothesis that CHIMERA TBI induces inflammation, white matter pathology, and A-beta deposition in acute post-injury period. Future studies will reveal how CHIMERA TBI affects disease progression in APP/PS1 mice.

Keywords: Novel TBI Model, Mild TBI, APP/PS1 Mouse Model of AD, Inflammation, White Matter Pathology

D2-10

DYNAMIC PROFILING: OUTCOME PREDICTION IN TBI BASED ON DEMOGRAPHICS, INJURY CHARACTERISTICS, AND INFLAMMATORY MEDIATORS

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Objectives: Inflammation induced by traumatic brain injury (TBI) can lead to both morbidity and mortality. The goal of the present study was to develop dynamic, data-driven computational models in order to predict the likelihood of mortality post-TBI.

Methods: Thirteen inflammatory cytokines and chemokines were determined using Luminex™ in serial cerebrospinal fluid samples from 31 TBI patients (26 survivors [24 males/2 females] and 5 non-survivors [4 males/1 female]). Overall, patients in the cohort were 33 ± 3 years old, with a mean Glasgow Coma Scale (GCS) score of 6 ± 0.2. Data on each subject, consisting of ten clinical (one-dimensional) variables, such as age, gender, GCS score, Glasgow Outcome Scale (GOS) score, and presence of infection, along with inflammatory mediator time series were used to develop a technique called ''Dynamic Profiling''. Dynamic Profiling attempts to recreate the clinician's decision making process, by clustering patients sequentially over time with regard to likelihood to die, using Hartigan's k-means method, into disjoint groups at different stages based on demographic, injury, and inflammation data.

Results: Using the Dynamic Profiling method, we could segregate patients over time with regard to their mortality odds. This model had a predictive accuracy of 72% for non-survivors.

Conclusions: A novel, data-driven method was developed to assess the probability of morbidity and mortality following TBI. This method incorporates both injury-specific and demographic data as well as a broad panel of inflammatory markers. Outcome prediction in the setting of TBI may be improved by use of the Dynamic Profiling method, which in essence replicates physician decision making in the setting of TBI.

Keywords: Dynamic Profiling

D2-11

DIFFERENTIAL DYNAMIC NETWORKS OF INFLAMMATION IN CEREBROSPINAL FLUID OF TRAUMATIC BRAIN INJURY SEGREGATE SURVIVORS & NON-SURVIVORS

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Objectives: Though inflammation induced by traumatic brain injury (TBI) is a mediator of morbidity and mortality, its complexity has defied therapeutics and diagnostic applications. We have previously suggested that inference of dynamic inflammation networks may aid in filling this gap. Thus, we hypothesized that differential dynamic inflammation programs characterize TBI survivors vs. non-survivors.

Methods: Thirteen inflammatory cytokines and chemokines were determined using Luminex™ in serial cerebrospinal fluid (CSF) samples from 31 TBI patients over 5 days. In this cohort, 5 were non-survivors (Glasgow Outcome Scale [GOS] score = 1) and 26 were survivors (GOS > 1). Significant differences in the time courses of CSF inflammatory mediators were determined by Two-Way ANOVA. Principal Component Analysis (PCA) was used to identify signatures and key drivers of the inflammatory response. Dynamic Bayesian Network (DyBN) inference was used to define central nodes of positive/negative feedback, as well as defining outcome-specific dynamic interrelationships among inflammatory mediators.

Results: A Pearson correlation analysis of GCS vs. GOS suggested that survivors and non-survivors had distinct clinical response trajectories to injury. Statistically significant differences ($p < 0.05$) in interleukin (IL)-4, IL-5, IL-6, IL-8, IL-13, and tumor necrosis factor-α (TNF-α) were observed between TBI survivors vs. non-survivors by Two-Way ANOVA. PCA suggested that IL-6 and IL-8 were hallmarks of the post-TBI inflammatory response, whereas macrophage inflammatory protein-1α (MIP-1α) and IL-10 were key component of the inflammatory response in non-survivors. DyBN inference suggested a core module of self-feedback and cross regulation among IL-6, IL-8, and IL-1α in TBI survivors, with multiple mediators such as TNF-α and IL-1β as output nodes. In contrast, DyBN suggested that IL-6 and IL-8 alone were central nodes in TBI non-survivors.

Conclusions: Differential dynamic trajectories and network patterns elucidated by *in silico* modeling highlight the importance of IL-6 and IL-8 as principal drivers and central nodes in both survivors and non-survivors following TBI, with a potential role for IL-1α in survivors.

Keywords: TBI

D2-12

DEVELOPMENT AND CHARACTERIZATION OF A ZEBRAFISH MODEL OF TBI

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Background: Traumatic brain injury (TBI) is a leading cause of death and morbidity in industrialized countries with considerable associated direct and indirect healthcare costs. Animal models have been critical in efforts to understand the pathophysiology of TBI, and to aid in the identification of novel therapies. To date, numerous models of closed-head trauma have been developed to address mTBI sequelae. However, even with the use of rodent models, preclinical drug evaluation is a lengthy process. In this regard, the zebrafish (ZF) has numerous advantages to address the technical and time-dependent obstacles associated with preclinical drug validation. There is a high degree of evolutionary conservation between ZF and human homologue proteins, brain structures, and pathways. Furthermore, ZF offer advantages compared with other vertebrate models, including the availability of rapid and efficient tools for genetic manipulation and significant potential advantages in live imaging and documentation of injury progression.

Methods: We developed and characterized a ZF model of TBI designed for high-throughput drug screening. In adult zebrafish, a

targeted 1-MHz pulsed high intensity focused ultrasound (pHIFU) system was applied to adult ZF to create the first closed-head injury model in ZF.

Results: Automated behavioural testing and Western blot analysis of susceptible white matter proteins expression demonstrated dose-dependent response to ultrasound injury. The model also demonstrated responsiveness to two interventions (hypothermia and hypoxic preconditioning) shown to be effective in other models of TBI.

Conclusions: Our results indicate that the ZF response to brain trauma exhibits similar mechanisms of secondary injury to mammalian pathophysiology. Our model can be used to rapidly screen potential therapeutic candidates. This is an important novel tool for investigating the mechanisms of downstream neuronal death, and for the rapid implementation of large-scale preclinical drug evaluation for TBI.

Keywords: Zebrafish

D2-13

IMMUNE CELL ACTIVATION UNDERLYING LEARNING AND MEMORY IMPAIRMENT IN THE JUVENILE FEMALE RAT AFTER REPEAT CLOSED HEAD INJURY

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It is well understood that sustaining multiple mild traumatic brain injuries (mTBI) can increase risk for suffering more persistent and severe symptoms, yet the physiological cause of this increased risk remains unclear. Recent work on this problem has focused primarily on adult male subjects, despite clinical evidence suggesting that that mTBI outcomes may be worse in females and in children. To investigate this critical issue in these populations of interest, we developed a clinically-relevant closed head injury model to induce repeat mild traumatic brain injury in rodents. This model was used to induce single and repeat mTBI in juvenile female rats in order to characterize the pathophysiological processes underlying learning and memory impairment, a common mTBI symptom. Postnatal day 25–28 female rats received a single closed head mTBI, or four mTBIs over 26 hours, and a control group received sham mTBIs. Spatial learning and memory were assessed in the Morris water maze on the second to seventh day after the final impact. At seven days post-impact these rats were sacrificed and their brains were extracted for histological assessment. FluoroJade-C staining and caspase3 immunohistochemistry were used to detect necrotic and apoptotic cell death in the hippocampus. Immunohistochemical staining of GFAP and Iba1 were used detect activation and recruitment of astrocytes and microglia, respectively, in the hippocampus. Preliminary findings show that repeat mTBI leads to impaired learning and memory in the Morris water maze, accompanied by immune cell activation and cell death in the hippocampus. These findings show that this closed head injury model is able to reliably produce mTBI symptoms and pathology that reflect those seen in clinical populations. Future investigations will characterise a time course of these processes in the first week after single and repeat mTBI.

Keywords: repeat mTBI, closed head injury, learning and memory, pediatric mTBI

D2-14

MECHANICAL RESPONSE OF SWINE EXPOSED TO FREE-FIELD BLASTS

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The mechanism of blast induced traumatic brain injury (BTBI) is not well understood. BTBI caused by explosion represents the response of brain to the initial blast waveform. Experimental data on live animals provides indispensable information of brain neurotrauma caused by blast exposure. However, there is little knowledge on the biomechanical responses of the brain subjected to primary free-field blast waves in large *in vivo* animal models. This study presents a swine model of primary blast injury to the brain. The incident blast overpressure (IOP) was generated using 8 lbs of C4 charges detonated at various stand-off distances to the forward facing anesthetized male Yucatan swine (50–60 kg, ages 6–8 months). The average peak IOP in the three free-field blast groups were 148.8 kPa (low), 278.9 kPa (medium), and 409.2 kPa (high). The mechanical responses of the brain were recorded with intracranial pressure (ICP) sensors placed on the surface of the brain at 4 locations (frontal, parietal, left and right temporal, occipital lobe) and the center of the brain. The head kinematics were recorded with tri-axial linear accelerometers and tri-axial angular rate sensors installed on a block with rigid attachment to the skull. ICP peak values (94–140 kPa, 210–282 kPa, and 312–420 kPa) at the various brain locations were increased with IOP levels. Nonetheless, there was no significant difference in peak values at different locations of the brain at the same IOP level. Peak resultant head acceleration (175–636 g) correlated well with peak IOP. The durations of the linear acceleration and angular velocity were typically less than 3 ms with very little head motion. The results of this model provide initial detailed response data of swine brain during exposure to primary blast waves. The experimental data can be used to validate computer models. When combined with injury data in parallel studies the ICP responses at different blast levels can be used to help determine injury mechanisms and thresholds of the brain subjected to primary blast.

Keywords: Primary blast induced brain injury, Swine model, Open-field blast, Intracranial pressure measurement, Head acceleration and velocity,

D3 Poster Session VII - Group D: Neurotransplantation

D3-01

SURVIVAL AND BIODISTRIBUTION OF HUMAN FETAL NEURAL STEM CELL TRANSPLANTS IN PENETRATING BALLISTIC BRAIN INJURY (PBBI)

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Introduction: Penetrating traumatic brain injuries (PTBI) are associated with the worst outcomes with both high mortality and severe disability. While no treatment strategies are available, neural stem cell transplantations have emerged as putative therapeutic approach. In this rodent study, we evaluated the biodistribution of FDA approved human fetal neural stem cells (hNSC; Neuralstem Inc.) in a rat model of PTBI: Penetrating ballistic brain injury (PBBI).

Methods: Adult Sprague-Dawley rats underwent a unilateral penetrating ballistic brain injury (PBBI). Immunosuppression was es-

tablished before stereotactic injection of control or green fluorescent protein (GFP) expressing hNSCs into the PBBI penumbra one week later. Animals were sacrificed at defined time points post-transplantation. Brains were sectioned and assessed for GFP fluorescence.

Results: The cells at week 1 post transplantation were undifferentiated and morphologically indistinguishable from undifferentiated cells *in vitro*. By week 5, a robust transplant could be seen sending out processes as far as 2–3 millimeters. By week 8 the number of processes was greater and they could be observed in the hind brain ($\sim$12 mm from transplant site). The GFP processes emanating from the transplant appear to follow intact white matter tracts in PBBI brain. The processes were found to cross internal capsule in ipsilateral hemisphere and traverse corpus callosum into contralateral hemisphere.

Conclusion: PBBI is conducive to human fetal neural stem cells engraftment and survival. The transplanted cells appear to be capable of sending processes over long distances.

Support: This work was supported by State of Florida funding.

Keywords: Penetrating traumatic brain injury, Neural stem cell transplants, FDA, Neurogenesis, Light sheet microscopy

D3-02

TRANSPLANTATION OF HUMAN INDUCIBLE PLURIPOTENT STEM CELL-DERIVED NEURAL STEM CELLS PROMOTES LOCOMOTOR RECOVERY AFTER SCI

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Transplantation of hiPSC-derived neural stem cells (NSCs) could be one of the most promised novel reparative strategies to promote functional recovery after spinal cord injury (SCI). One of the major challenges to fully realized the full therapeutic potential of hiPSC is to purify the desired NSCs from differentiating hiPSCs in vitro before transplantation. In this study, we use the neural stem cell specific hiPSC reporter line and fluorescence-activated cell sorting (FACS) to purify NSCs and then test its therapeutic potential for SCI. The nestin-EGFP reporter hiPSCs, in which EGFP cassette has been inserted to the nestin locus of hiPSC via homologous recombination, are induced for neural differentiation and GFP expressing NSCs are purified by FACS. The purified cells express NSC but not iPSC markers. Importantly, the purified NSCs continue to proliferate for a long time in vitro and differentiate into neurons, astrocytes and oligodendrocytes under respective differentiation conditions. NOD-SCID mice receive moderate contusion at T9 and then grafts of hiPSC-derived NSCs, human fibroblasts or control medium at 8 days after SCI. Robust survival of grafted NSCs is observed in all animals receiving grafts at 2 months after transplantation. Some grafted NSCs differentiate into NeuN+ mature neurons and more into doublecortin+ immature neurons. Astrocyte or oligodendrcoyte differentiation is also observed in grafted NSCs. The volumes of spared white and gray are significantly increased in animals received NSC graft. Furthermore, recovery of hindlimb locomotor function is significantly enhanced in animals receiving grafted of hiPSC-derived NSCs. No teratoma formation is observed in any animals receiving hiPSC-derived NSCs. Our results show that the multipotential NSCs can be purified from NSC specific reporter hiPSC line by FACS. Importantly, purified NSCs can survive and differentiate into both neurons and glias and promote functional recovery after transplantation following traumatic SCI. These results suggest that hiPSC-derived NSCs have great therapeutic potential for SCI and other neurological diseases.

Keywords: spinal cord injury, neural stem cell, hiPSC

D4 Poster Session VII - Group D: Transplantation

D4-01

INTRACEREBROVENTRICULAR TRANSPLANTATION OF ADULT NEURAL STEM CELLS (NSCS) AFTER TBI: PROOF-OF-CONCEPT FOR ACTIVATION OF HOST NSCS

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Transplantation of neural stem cells (NSCs) may promote brain repair by replacing lost cells and by interacting with the host tissue to modulate the immune response and stimulate endogenous regenerative capacity. Determining an effective NSC delivery route in the CNS is particularly challenging for TBI that involves diffuse rather than focal lesions. In clinical management of TBI, ventriculostomy is often performed in patients with acute TBI after failure to control intracranial pressure by other means. Ventriculostomy may provide a route of access to the lateral ventricle for therapeutic delivery of stem cells. The current studies provide a proof-of-concept test of intracerebroventricular (ICV) delivery of adult NSCs into the lateral ventricle in an impact-acceleration TBI model with traumatic axonal injury in the corpus callosum. We also test the effect of NSC transplantation in stimulating a regenerative response in endogenous NSCs in the host subventricular zone (SVZ) based on activation of Sonic hedgehog (Shh) signaling. Shh maintains the NSC niche in adult CNS. Gli1 transcription indicates active Shh signaling. TBI from impact to the skull at bregma was produced in adult *Gli1CreERT2* mice crossed to *RosaTdTomato* reporter mice. NSCs were isolated from adult *UBI-GFP* mice, which ubiquitously express green fluorescent protein (GFP), and microinjected unilaterally into the lateral ventricle of the *Gli1CreERT2;RosaTdTomato* mice 2 weeks after the TBI or sham procedure. *Gli1CreERT2;RosaTdTomato* host mice were then administered tamoxifen to label endogenous cells responding to Shh signaling after ICV transplantation. Mice were sacrificed for tissue analysis at 4 weeks post-TBI. Transplanted GFP-NSCs survived, maintained an immature phenotype, and were localized along the ependymal lining of the ventricle and adhering to the choroid plexus. Endogenous NSCs in the adjacent SVZ were fate-labeled with TdTomato, indicating active Shh signaling, but were not changed significantly due to the injury or ICV transplantation of GFP-NSCs. An inflammatory response to transplanted GFP-NSCs was not observed in sham or TBI mice. Funded by the DoD in the Center for Neuroscience and Regenerative Medicine (CNRM).

Keywords: Transplantation, neural stem cell, Sonic hedgehog

D4-02

DIFFERENTIATION OF FDA-APPROVED HUMAN NEURAL STEM CELLS WITH FUNCTIONAL IMPROVEMENT AFTER A PENETRATING TBI

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Introduction: Penetrating traumatic brain injuries (PTBI) are associated with the worst outcomes with both high mortality and severe disability. While no treatment strategies are available, stem cell transplantations have emerged as putative therapeutic approaches. In this rodent study, we evaluated the differentiation of FDA approved human fetal neural stem cells (hNSC; Neuralstem Inc.) in a rat model of PTBI.

Methods: Adult Sprague-Dawley rats underwent a unilateral penetrating ballistic brain injury (PBBI). Immunosuppression was established before stereotactic injection of control or hNSCs into the PBBI penumbra one week later. Motor function was evaluated using the rotatrod. Animals were sacrificed at defined time points post-transplantation. Brains were sectioned and assessed for cell maturation and evidence of new synapses using immunohistochemistry.

Results: Using markers for immature and mature neuronal markers, we determined that transplanted cells displayed a predominantly neuronal phenotype. Neuronal cells were observed in the thalamus, hippocampus and cortex at later time-points. Immature neurons with simple processes as well as mature neurons with complex dendritic arborizations were observed projecting towards the PBBI lesion. Using the rotarod, animals with transplant performed better at fixed speeds (10, 15 and 20 rpm) compared to injured controls.

Conclusion: Robust engraftment of NSCs is seen following a PBBI Transplanted cells differentiate towards a neuronal lineage Cell transplantation results in improved motor performance post-injury

We conclude that NSC transplants may offer a potential treatment for PTBI.

Keywords: Human Stem Cells, Penetrating Injury, Axonal Growth, Immunosuppression

D5 Poster Session VII - Group D: Monitoring

D5-01

CAN CEREBRAL MICRODIALYSIS USEFULNESS BE EXTRAPOLATED TO CLINICAL PROGNOSTICATION ASSESSMENT IN SEVERE TRAUMATIC BRAIN INJURY ?

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Introduction: Secondary brain insult post TBI occurs as a result of cerebral ischaemia and is preventable. Cerebral MD provides a method of measuring parameters predicting cerebral ischemia/mitochondrial dysfunction before clinical signs.

Materials: A non randomized prospective cohort of 19 sTBI patients aged 22–45 years (16 males/3 females) were analysed to evaluate use of metabolic parameters in predicting outcome and to distinguish between ischemia and mitochondrial dysfunction. All patients underwent decompressive craniectomy with placement of MD catheters in peri-contusional tissue, monitored on an hourly basis for 3–5 days. Ischemia was identified with LP ratio > 25 with low pyruvate levels and mitochondrial dysfunction as high LP ratio > 25 with near normal pyruvate levels.

Observations: Eleven patients (58%) had good GOS at 3 months outcome while 8 patients had poor GOS (3) outcome. Consistently high LP ratios were noted in peri-contusional tissues (range: 19.5 to 134). Average glucose values ranged from 0.5 to 4.2, mean 1.7 mmol/l. Average glycerol values showed maximum variation ranging from 14 to 1395 with a mean of 314. Average ICP ranged from 11.7 to 29 mmHg.

Outcome: Variables were assessed as predictors of GOSE at 3 months. None of metabolic parameters evaluated i.e., Glutamate, Lactate, Pyruvate, Glucose, Glycerol and CPP could be predictive of outcome. LP ratio between two groups also did not show significant difference ($p = 0.09$).

Conclusions: Our study shows cerebral MD values for glucose similar to international standards. Higher value of MD parameters noted in present series may be explained by the use of MD only in patients undergoing a decompressive craniectomy indicating a higher level of insult. Cerebral MD variables glutamate, glycerol, lactate, pyruvate, glucose and CPP were not individually predictive of outcome at 3 months. It seems the primary insult seems to be the prime factor-predicting outcome.

Keywords: Cerebral Microdialysis, Traumatic Brain injury, Ischemia, MItochondrial dysfunction

D5-02

DETECT: A NOVEL TOOL FOR FIELD ASSESSMENT OF CONCUSSION

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Current protocols for on-field concussion evaluation are largely subjective and unreliable. The Display Enhanced Testing for Cognitive Impairment and mTBI (DETECT) device is an objective tool for rapid neuropsychological testing (NPT) after suspected concussion. The objective of this study was to determine the ability of DETECT to accurately assess neurocognitive deficits associated with concussion. DETECT was implemented over the course of a single season of two high school and two college football teams. Athletes pulled from play for suspected concussion were tested with DETECT immediately following athletic trainer assessment. DETECT scores were compared with the clinical diagnosis of concussion (reference standard) and NPT tools employed at each institution. A total of 131 athletes completed baseline testing. Twenty-one players were tested for suspected concussion; 15 met the reference standard definition of concussion. DETECT was 86.7% sensitive (95% CI: 59.5%, 98.3%) and 66.7% specific (95% CI: 22.3%, 95.7%) in correctly identifying concussed athletes. In a mixed cohort of football players with and without suspected concussion ($n = 90$), DETECT was 92.9% sensitive (95% CI: 66.1%, 99.8%) and 43.4% specific (95% CI: 32.1%, 55.3%) for cognitive impairment after concussion. Thirty-three players completed post-injury ImPACT testing as a part of their return-to-play protocol. DETECT demonstrated a fair, yet statistically relevant, agreement with ImPACT outcomes in the post-injury period ($k = 0.33$, $p = 0.03$). DETECT confers moderate to high sensitivity in identifying acute cognitive impairment iconcussion, and demonstrates fair agreement with more traditional NPT tools. Given the need for more objective concussion screening in triage situations, DETECT may provide a new solution for mTBI assessment and management decisions. Funded by U.S. Army MRMC W81XWH-12-C-0203

Keywords: Concussion, Neuropsychological Testing

D5-03

TEST-RETEST REPEATABILITY AND REPRODUCIBILITY OF MULTI-MODAL TESTING IN 3D HEAD MOUNTED DISPLAY (HMD) WITH EYE TRACKING SYSTEM

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Mild traumatic brain injury (mTBI) is a public health concern garnering increased public attention. Neurosensory effects are among the most common sequella seen after mTBI, specifically balance-related issues. Acute mTBI patients can be identified with greater than 85% sensitivity and specificity utilizing a multi-modal battery of tests; including oculomotor, vestibular, and reaction time tests.

Ongoing DOD trials using a multi-modal test battery on a neuro-otologic test center demonstrate positive results. The device is not portable and is in clinics that are far from site of event. This delays diagnosis and possibly reduces an individual's recovery. Utilizing a portable goggle system with high speed eye tracking and 3D integrated stimulus display can resolve this problem, with an evaluation of an mTBI in the absence of a clinical setting.

The I-Portal®-Portable Assessment System (I-Portal PAS), developed by Neuro Kinetics, Inc. (NKI), provides the means to present a 3D HMD stimulus, and measures variables of ocular motility, vestibular and reaction time tests.

A test-retest repeatability analysis was performed at the Vestibular laboratory at Bloomsburg University. Thirty individuals participated in this evaluation. These participants were tested three times utilizing randomized test protocols with three sets of PAS goggles. The time between the sessions, protocol sequences and operators were varied to evaluate the repeatability of the test protocols.

Variables for individual tests were collected, e.g. saccadic latencies, accuracies, and velocities; pursuit gain, asymmetry and percentage of saccadic intrusion, optokinetic gains, pupil constriction velocity, average and peak slow phase velocity. Results from each were compared for test-retest repeatability, reproducibility and internal consistency utilizing SPSS 21, IBM.

The analyses revealed that this multi-modal test battery utilizing a portable 3D HMD system with integrated eye tracking generates results that are repeatable and reproducible and are not related to testers or specific versions of the device.

Keywords: assessment, portable, mTBI, multi-modal

D5-04

NEUROSENSORY SYMPTOMS COMPLEXES AFTER ACUTE MILD TRAUMATIC BRAIN INJURY

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Study Objectives: Mild traumatic brain injury is an increasingly common public health issue. A great deal of work remains to be done detailing the consequences of this injury and optimizing the management of this disorder. The objectives of this study were to examine the type and relative frequency of neurosensory symptoms seen after acute mild traumatic brain injury (mTBI).

Methods: Fifty individuals with acute mild traumatic brain injury (ages 18–45 years of age) were compared to 100 matched controls. Acute patients were seen on average less than 48 hours after mTBI and no more than six days after the event. Assessment of neurosensory symptoms was performed using a structured history and physical, specific balance and cognitive tests, standardized instruments, and detailed balance testing.

Results: Detailed analysis of this group of patients demonstrated that neurosensory symptoms could be divided into five domains as follows: dizziness, emotional, fatigue, headache and nausea. All of these domains were significantly different in the TBI group as compared to controls. The subjective complaints correlated with particular instruments or tests used in standard mTBI evaluation panels but not each domain was predicted by every standard test.

Conclusions: Neurosensory symptoms are the most common symptom of mTBI and are among the easiest symptoms to characterize in the acute phase of this disorder. Understanding the neurosensory symptoms complexes and how best to evaluate them has enormous implications for the management of mTBI and may prove to be a key diagnostic tool for injury detection as well as return to work/play guidelines.

Keywords: traumatic brain injury, diagnosis, neurosensory symptoms, management

D5-05

CONDITIONED LOCOMOTION FOLLOWING THORACIC SCI IN RATS: COMPARATIVE ASSESSMENT OF GAIT ANALYSIS USING AUTOMATED DEVICES

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A number of automated devices exist to evaluate conditioned locomotion in rodents after spinal cord injury (SCI). However, it remains unclear which of these is most sensitive, reliable and reproducible in providing injury and treatment-related data for gait analysis. In this study, we subjected adult female Fischer rats to a T8 thoracic SCI using the MASCIS impactor at a moderate severity (12.5 mm) or a severe severity (25.0 mm) versus sham controls. At 9 weeks post injury, locomotor function was evaluated using the Basso, Beattie, Bresnahan (BBB) score, the Catwalk device or the Kinetic Weight Bearing (KWB) apparatus. The Catwalk provides measurement of 208 gait parameters, of which 77 (37.01%) showed a difference in at least 1 pairwise group comparison, 51 (24.51%) showed a difference in at least 2 pairwise group comparisons, and 10 showed a difference in all pairwise group comparisons. The KWB measures 64 gait parameters, of which 13 (20.31%) showed a difference in at least 1 pairwise group comparison, 10 (15.6%) showed a difference in at least 2 pairwise group comparisons, and 5 showed a difference in all pairwise group comparisons. Hierarchical Cluster analysis was then employed to evaluate the reliability of each device. The Catwalk gait analysis data showed that 81.2% of animals are clustered correctly with their original group assignments, followed by the BBB score (76.4%) and the KWB (52.9%). The coefficient of variation (CV) was next used to evaluate the reproducibility of each test for measuring changes in locomotion. For the moderate SCI group, the severe SCI group and the sham group, respectively, the BBB score had CVs of 0.07, 0.05 and 0, the KWB had CVs of 0.157, 0.165 and 0.157, while the Catwalk had CVs of 0.267, 0.286 and 0.220. Conclusion: It appears that the Catwalk device is the most sensitive and reliable for automated gait analysis to evaluate locomotor function after thoracic SCI in rats.

Keywords: catwalk, Kinetic Weight Bearing, locomotion, gait analysis, the Basso, Beattie, Bresnahan (BBB) score

D5-06

RELATIONSHIP OF SIMULTANEOUSLY RECORDED VENTRICULAR AND PARENCHYMAL INTRACRANIAL PRESSURE

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Evidence has shown that decreased cerebral perfusion pressures are correlated with poor outcomes in traumatic brain injury. Reliable CPP measurements depend on continuous mean arterial pressure and intracranial pressure measurements. Current Brain Trauma guidelines recommend intracranial pressure monitoring in all traumatic brain injured patients with a GCS of 3–8 with an abnormal CT scan. Furthermore, treating elevated intracranial pressures without monitoring has potential risks and has shown to be deleterious. While both parenchymal and ventricular monitors are widely used, each has its own advantages and drawbacks with selection depending on a host of factors. Our institution, University of New Mexico Hospital, recently published its 5 year experience with the Hummingbird Monitoring system (InnerSpace Medical), a multi-modality monitoring system that provides a multi-port device allowing for both parenchymal and ventricular ICP monitors as well as for tissue oxygenation and cerebral blood flow measurements from within the adjacent deep white matter. All data is acquired via the Component Neuromonitoring System (CNS, Moberg Technologies). The availability of both types of ICP readings has allowed for optimal management of a TBI patient in which CSF can be drained from the ventricular drain while still measuring the intracranial pressure from the parenchymal monitor. The continuous stream of dual ICP measurements makes it possible not only to determine the precise relationship between parenchymal ICP and ventricular ICP but also to determine quantitative values regarding the effects of CSF drainage on ICP. From analyzing $\sim$30 TBI patients we show that the intraparenchymal pressures are, on average, slightly lower than the ventricular pressures. We also demonstrate that CSF drainage, resulting in a decrease in ICP, can correlate with an increase in tissue oxygenation. In recent literature, the validity of intracranial monitors in TBI patients has come under question. With the above findings, we believe that there is a spectrum of TBI physiology between which a multi-modality system can help differentiate.

Keywords: Multimodal, EVD, parenchymal, ventricular, drain, ICP

D5-07

SYMPTOMOLOGY OBSERVED IN HUMANS FOLLOWING ACUTE EXPOSURE TO EXPLOSIVE BLAST

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Exposure to explosive blast clearly presents risk for neurotrauma but blast magnitude, number, or frequency that represents threshold for injury remains unknown. Among studies involving human subjects, there is a series of studies on personnel exposed to repeated blast as a condition of their occupation. These professionals do not accrue clinical diagnosis from occupational blasts, but a previous study showed that they report symptomology consistent with concussion and that correlates with degree of blast exposure. To examine with prospective data, the present study assessed acute symptom endorsement at timepoints across a series of exposures to blast. Thirty-two military personnel completed a daily assessment battery during a 10-day training protocol that included use of explosives in close proximity. A key outcome measure was a 32-item symptom checklist with 5-level Likert scale responses. Outcome measures also included postural stability, cognitive performance, sleep, and a blood-based neurotrauma biomarker. Blast was recorded with pressure gauges worn by each individual. Symptoms following acute exposure to blast were similar to those previously reported with chronic exposure. The prospective design revealed that not all blast exposures were associated with change in symptom reporting. Symptoms were elevated following only the largest blast, with recorded peak overpressure ranging from 5 to 12 psi across individuals. Daily symptom reporting mapped more closely to blast magnitude than did other outcome measures. Effects of blast in standard training protocols are expected to be small, if present at all, given that this type of blast exposure is not known to result in diagnosed injury, medical aid, or removal from training. Effects may have similarity to subconcussive hits in contact sports. Until a reliable biomarker for mild neurotrauma becomes available, self-report symptomology may be the best indicator for effects on the brain from low level blast.

Keywords: blast, symptomology, military, subconcussive

D6 Poster Session VII - Group D: Rehabilitation

D6-01

SPONTANEOUS FRACTURE OF CRANIOPLASTIC TITANIUM IMPLANTS WITHOUT HEAD TRAUMA IN AN ADULT: A CASE STUDY

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The cranioplasty is a classical surgical procedure carried out to repair large skull defects. The most current cranioplasty using computer-based design and modeling implants provides the best results to meet both cosmetic and functional requirement of patients. So far, the titanium is the only metal implants used, which features multiple advantages, including strong strength and malleability. In the current report, we documented the first case of cranioplastic titanium mesh implant fracture at the frontal-parietal-temporal locus, which occurred 13 months postoperatively without any trauma or extra force on the head. Additionally, the implant was detached from the basitemporal locus. A second cranioplasty was performed and the follow-up result was unremarkable at 8 month post-second-operation. This case is the first reported incidence of spontaneous fracture of titanium mesh implant without extra force on head in an adult.

Keywords: fracture; cranioplastic; titanium; implants

D6-02

EXAMINATION OF STEPPING AND TAIL OSCILLATIONS AS A RESULT OF TEMPORAL RELATIONS AND FREQUENCY

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Our laboratory has shown that the spinal cord is sensitive to temporal relations. Specifically, stimuli presented in a regular (fixed, FT) or

irregular (variable, VT) spaced manner have divergent effects on spinal cord plasticity. Six minutes of VT shock produces a maladaptive effect that inhibits adaptive plasticity. In contrast, extensive training with FT shock promotes adaptive plasticity and reverses and prevents the effects of variable spaced stimulation. Recently, our lab provided evidence that the beneficial effects of fixed spaced shock depend upon the central pattern generator (CPG) within the lumbar enlargement. Given the role of the CPG in locomotor behavior, we examined whether the temporal distribution of shocks would differentially affect locomotion. Two minutes after an intrathecal injection of serotonin (5HT) and NMDA, transected rats received 720 shocks in either a VT (0.2–3.8 s) or FT (every 2 s; 0.5 Hz) shock pattern. Unexpectedly, some subjects that received FT shock began to move their tail in an oscillating fashion. Tail movements continued even after shock ended and had moved at the same frequency. Further, examination of the tail movement during FT shock showed evidence of anticipatory behavior (movements before next shock presentation), reminiscent of temporal conditioning. Finally, the amount of stepping was dependent on the temporal pattern received. We next examined the effects of frequency (0.5, 2, or 8 Hz) on stepping and tail movement. We found higher frequencies produced the highest amplitude tail oscillations. Peak oscillation frequencies were observed at 0.5 and 2 HZ, regardless of stimulation frequency. Finally, we examined temporal conditioning by systematically skipping a shock (producing a 4 second pause) every 60 shocks during FT or VT shock. Tail movements during the 4-second pause showed increased tail amplitudes around the time of missed shock in the FT group. These observations provide evidence for an oscillatory mechanism underlying the FT effect, which may be important for enhancing locomotor behavior.

Keywords: Tail Movement, Stimulation, Learning, Locomotion

D6-03

IMPACT OF AEROBIC EXERCISE ON COGNITIVE FUNCTIONS IN AN AGING MILD TRAUMATIC BRAIN INJURY POPULATION: A PILOT STUDY

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Effects of mild traumatic brain injuries (mTBI) are most evident with aging, as mTBI victims are more at risk of experiencing mild cognitive impairment. Moderate levels of physical activity have been associated with a reduced risk of developing dementia. This study aims to evaluate the impact of aerobic exercise in an aging mTBI population.

Methods: Twelve participants, aged between 55 and 70 and having sustained a mTBI two to seven years earlier, were recruited to participate in a three month physical exercise program. They were divided into two groups: aerobic training (on cycle ergometers) and a control group (stretching exercise). The participants' cognitive functions (neuropsychological testing) and physical condition (cycling tests) were evaluated before and after the training.

Results: The present study shows that participants from the aerobic exercise group significantly improved their peak exercise capacity ($F = 10.42$, $p < 0.05$)) and their performances on different neuropsychological tests, including the Trail Making Test Part B ($F = 2.57$, $p = 0.14$) and the Brief Visuospatial Memory Test - Revised ($F = 7.69$, $p < 0.05$), when compared to participants from the control group. Furthermore, correlations drawn between these measures showed that the participants who most improved their peak exercise capacity were also those who showed the biggest improvements on neuropsychological measures: Trail B ($R = -.632$, $p = 0.03$) and BVMT-R ($R = .411$, $p = 0.18$).

Conclusion: These results demonstrate the importance of considering aerobic exercise as a relevant intervention to improve cognitive functioning of mTBI patients.

Keywords: aerobic exercise, mild traumatic brain injury, neuropsychology, nonpharmacological intervention

D6-04

EFFECT OF COGNITIVE REHABILITATION IN IMPROVING COGNITIVE SYMPTOMS AND DIFFUSION TENSOR IMAGING FINDINGS FOLLOWING MILD TBI

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Aim: This study is to evaluate the effectiveness of cognitive rehabilitation therapy in the alteration of neuropsychological performance and Diffusion Tensor Imaging (DTI) parameters in mild traumatic brain injury (mTBI).

Method: An interventional study of 6 months. MTBI patients with normal computed tomography brain scan finding and had fulfilled inclusion criteria, underwent structural DTI scan within 10 hours post trauma and evaluated using Screening - Neuropsychological Assessment Battery (S-NAB Form 1) within two weeks of injury. Patient education session and self-monitoring of symptoms were implemented, followed by individualized cognitive therapy, based on baseline deficits of neurocognitive performance. Computerized therapeutic rehabilitative tools were used, along with customized patient items. Frequency of therapy is weekly with 3 months post injury review of progress by using S-NAB (Form 2). At six months, all participants underwent repeat DTI MRI scan and S-NAB and the results compared with baseline.

Results:15 patients with mTBI (mean age 27.12, SD 6.30) in the treatment group underwent DTI scanning at an average of 12.1 hours (SD 4.84) with neuropsychological performance assessment at an average of 8.25 hours (SD 7.08) upon full GCS recovery. Results were compared to 15 mTBI controls (who received standard treatment with a mean age = 28.15, SD 5.84). 86.8% of patients in the treatment group completed the individualized cognitive therapy and 66.7% of these patients made significant progress at 3 months post intervention. Stepwise improvement of neurocognitive performance at both 3 and 6 months post trauma were observed with corresponding recovery in few white matter tracts (66.7% in the treatment group and 40% in the control group).

Keywords: cognitive rehabilitation, diffusion tensor imaging, mild traumatic brain injury

D6-05

SYMPTOM ATTRIBUTION AFTER MILD TRAUMATIC BRAIN INJURY

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Over-attributing headache, fatigue, concentration difficulty and other symptoms to mild traumatic brain injury (MTBI), instead of benign causes such as daily stress, is thought to impede recovery. The present study examines symptom attribution after MTBI and its correlates. The sample consisted of highly symptomatic patients seeking treatment for MTBI at an outpatient concussion clinic 23.9 days (SD = 7.9) post-injury (N = 30; 60% female). As part of a clinical trial, a prognostic algorithm was applied to consecutive cases and only those at high risk for chronic symptoms were included. In the baseline assessment, participants completed the Rivermead Post Concussion Symptoms Questionnaire (RPQ) and then rated the degree to which each symptom was caused by their MTBI on a scale ranging from 0 (not at all) to 4 (entirely). Participants reported a median of 13 symptoms (IQR: 9 to 15) and attributed a median of 12 symptoms (IQR: 8 to 14) mostly or entirely to MTBI. One quarter of the sample (26.7%, n = 8) attributed every symptom to MTBI. Headaches, dizziness, nausea, slowed thinking, and double vision were virtually always (>95%) attributed to MTBI. Sleep disturbance and depressed mood were least often (80%) attributed to MTBI. RPQ total scores were associated with a higher number of symptoms attributed to MTBI ($r = .431$, $p = .017$) and a stronger degree of attribution ($r = .873$, $p < .001$). Adjusting for symptom severity, patients who attributed every one of their symptoms to MTBI were *less* anxious (Hospital Anxiety and Depression Scale = 7.48 vs. 11.33, $p = .025$, Cohen's $d = 0.61$), had similar expectations for recovery on the Illness Perception Questionnaire-Revised (14.09 vs. 15.60 $p = .352$, Cohen's $d = 0.25$), and were no more likely to be litigating ($\chi^2(1) = .29$, $p = .59$). In conclusion, patients who report more symptoms after MTBI tend to believe MTBI is the primary cause. However, over-attributing symptoms to MTBI was not associated with known risk factors for chronic post-concussion syndrome, and so may not be involved in the development of this condition.

Keywords: MTBI, Symptom Attribution, Concussion, Symptom Severity

D6-06

TEMPORAL PROFILE OF CARE FOLLOWING MILD TRAUMATIC BRAIN INJURY: PREDICTORS TO HOSPITAL ADMISSION, OUTPATIENT REFERRAL AND OUTCOME

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To date, guidelines for medical follow-up after mild traumatic brain injury (mTBI) are not defined, and better characterization of the temporal relationship between hospital admission, outpatient care, and recovery after mTBI is needed. We utilized the TRACK-TBI Pilot study to evaluate characteristics of mTBI patients 1) triaged to hospital admission, 2) referred to 3-month outpatient care, and 3) assessed with 6-month functional disability (GOSE < 7). Adult patients with GCS 13–15, Marshall Score 1–2, without neurosurgical intervention and alive at 6-months post-injury were included. Of 168 patients (age 44.5 ± 17.9 years, 69% male), 48% were admitted to hospital, 22% received outpatient care, and 27% reported 6-month functional disability. Intracranial lesion on CT (odds ratio (OR) 81.08, 95% CI [10.28–639.36]) and post-traumatic amnesia (>30 min-vs.- <30 min: OR 5.27 [1.75–15.87]; unknown-vs.- <30 min: OR 4.43 [1.26–15.64]) predicted hospital admission after adjusting for age, employment, anticoagulant use, and prior medical history (PMH). Age (OR 1.03 [1.00–1.05]) and employment (part-time/unemployed-vs.-full-time: OR 0.17 [0.06–0.50]) predicted 3-month outpatient referral after adjusting for gender and PMH. Education years (OR 0.86 [0.76–0.97]), GCS < 15 (OR 2.46 [1.05–5.78]), and PMH of seizures (OR 3.62 [1.21–10.89]) predicted 6-month functional disability after adjusting for psychiatric history. The analysis demonstrates that while clinical factors modulate triage to admission, PMH and socioeconomic factors modulate medical follow-up. Underlying reasons for this divergence need further clarification for better triage and resource allocation.

Keywords: Clinical Trial, Human Studies, Outcome, Mild TBI

D6-07

OPTIMIZING ENVIRONMENTAL ENRICHMENT TO MODEL PRECLINICAL NEUROREHABILITATION

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Traumatic brain injury (TBI) affects 1.7 million people in the USA each year. One therapeutic strategy that has been investigated is environmental enrichment (EE), which consists of a complex living space that confers cognitive and motor recovery when provided early and continuously after TBI vs. standard (STD) housing. Furthermore, 6-hours of EE/day introduced immediately after TBI is also sufficient to promote neurobehavioral recovery. However, these paradigms are not clinically ideal as patients, especially those with moderate-to-severe TBI, will not be able to engage in rehabilitation until after critical care has ended. Furthermore, once rehabilitation is initiated the duration of the therapy is limited, often ranging from 3–6 hours/day. Hence, refinement of the current model of EE such that it conforms more closely to that seen in real-world rehabilitation practice is a priority in order to advance a preclinical model of rehabilitation that can be applied to the TBI setting for implementation and assessment of therapies. Hence, to mimic the clinic, the goal of this study was to test the hypothesis that *delayed-and-abbreviated EE (i.e., rehabilitation) would confer similar behavioral benefits as early-and-continuous EE.* Anesthetized male rats were subjected to a cortical impact (2.8 mm depth at 4 m/s) or sham injury and randomly assigned to TBI + EE (continuous), TBI + EE (rehabilitation; i.e., 3-day delayed, 6-hr day), and respective sham controls. Motor function (beam-balance/beam-walk) was assessed on post-operative days 1–5. Spatial learning/memory (MWM) was evaluated on days 14–19. The data showed that EE, regardless of timing, improved motor and cognitive function compared to STD ($p < 0.0001$). Moreover, there were no differences between TBI + EE (continuous) and TBI + EE (rehabilitation); $p > 0.05$. These data demonstrate that delayed and abbreviated EE produces

motor and cognitive benefits similar to continuous EE after TBI, which supports the hypothesis and lends credence to EE as a preclinical model of neurorehabilitation. To further optimize the model, ongoing studies are evaluating longer delays in implementing EE after TBI.

Keywords: controlled cortical impact, environmental enrichment, preclinical model

D6-08

TELEPHONE PROBLEM SOLVING TREATMENT FOR ACTIVE DUTY SERVICE MEMBERS WITH MILD TRAUMATIC BRAIN INJURY:A RANDOMIZED CONTROLLED TRIAL

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During combat deployments service members (SMs) are at risk for sustaining mild TBI (mTBI) and experiencing persistent symptoms and co-morbid emotional and physical issues. Military duty demands, access to resources, and the stigma of treatment pose barriers to SMs receiving necessary care. Telehealth approaches can be effective in overcoming treatment barriers. Problem-solving interventions show promise for treating TBI-related issues. Our objective was to evaluate the efficacy of problem-solving therapy delivered by telephone on persisting distress and physical symptoms in active duty service members with combat-related mild traumatic brain injury (mTBI). We recruited 356 SMs with mTBI sustained while deployed and randomized them into one of two interventions: 1) telephone-based problem-solving treatment (PST); 2) TBI-education only (EO). Primary outcomes included the Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ) and the Brief Symptom Inventory (BSI-18). Secondary outcomes included additional measures of emotional and physical health and treatment satisfaction. Outcomes at 6-months post-enrollment were obtained for 89.9% of the sample and compared to baseline ratings. Mixed-effects regression suggested PST resulted in significant improvements over EO in emotional health (BSI-18 $p = .007$) but not post-concussion symptoms (RPCSQ $p = .182$). Secondary analyses revealed PST resulted in improvements over EO on other health-related ratings, including quality of sleep and depression, and that SMs preferred PST over EO. Therefore, telephone-based PST was acceptable and effective at reducing symptoms of emotional distress in SMs returning from deployment with mTBI.

Keywords: Military, Mild traumatic brain injury, Randomized controlled trial, Telehealth, Problem-solving treatment

D6-09

BRAIN-INITIATED EXERCISE PROGRAM PROMOTES GREATEST RECOVERY AFTER SCI

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Although rehabilitation is considered useful for spinal cord injury (SCI), non-brain-initiated rehabilitation may actually be detrimental by interfering with the re-organization of circuitry especially after interventions that stimulate repair. Recent studies find detrimental effects of passive stretch in SCI rats. Our goal is to directly compare two rehabilitation methods (exercises with and without brain initiation) to no rehabilitation in SCI. Our hypothesis is that the brain-initiated therapy program would be the most effective. Lewis rats ($n = 24$) with a T9 SCI (MASCIS device) were randomly assigned to three groups: 1. no rehabilitation; 2. non-brain-initiated exercises [passive stretch (20 min/day,5 days/week), motorized bicycle (15 min/day, 3 days/wk)]; 3. brain-initiated exercises [swimming (12 min/day, 2 days/wk); treadmill and ladder walking (30 min, 2 days/wk); environmental enrichment (1 hr/day, 2 days/wk)]. Outcome measures included BBB, inclined plane and beam tests. Muscle weight, levels of corticosterone using ELISA and number of newly generated hippocampal cells (Ki-67) were quantified. The brain-initiated exercise group demonstrated the most recovery in all functional tests while the non-brain-initiated exercise group performed worse than the no rehabilitation group. In the inclined plane test, the brain-initiated exercise group performed significantly better than the non-brain-initiated group at weeks 7 and 8 post-injury ($p = 0.017$). The mean extensor muscle weight was significantly greater in the brain-initiated exercise group than the other 2 groups. The mean flexor weights were again greatest in the brain-initiated exercise group but not significantly different. The corticosterone levels were similar in all groups. The brain-initiated exercise group had more newly generated hippocampal cells that may be an indicator of plasticity. The greater functional motor recovery with brain-initiated therapy supports the hypothesis that brain-initiated exercise is the best for functional recovery. Stress did not influence the results. Exercise in people that are not brain-initiated (passive stretch/ROM) may need to be modified and the cost-benefit ratio of robotics re-examined.

Keywords: exercise, plasticity, neurogenesis, spinal cord injury

D7 Poster Session VIII - Group D: Astrocyte

D7-01

THROMBIN PHOSPHORYLATES MYOSIN LIGHT CHAIN IN ASTROCYTES VIA THE RHO KINASE PATHWAY

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Background: The blood brain barrier (BBB) is compromised following neurotrauma and results in exposure of astrocytes to increased levels of serum proteins including thrombin. Thrombin activates astrocytes and microglia, and promotes further breakdown of the BBB. In endothelial cells the rho/rho kinase (ROCK) pathway is an important mediator of barrier integrity by regulating myosin light chain (MLC) phosphorylation. The role of ROCK and myosin light chain kinase (MLCK) in the mechanisms by which astrocytes maintain BBB integrity is not well understood. The aim of this study is to elucidate the role thrombin plays in MLC phosphorylation in astrocytes.

Methods: Primary cortical astrocytes were isolated from neonatal Sprague-Dawley pups. We exposed astrocytes to thrombin or specific PAR-1 agonist, and measured ROCK pathway activation and MLC phosphorylation. To determine the role for ROCK in MLC signaling we examined the effect of a rho kinase inhibitor on thrombin-induced MLC phosphorylation.

Results: Thrombin induced phosphorylation of MLC in a time-dependent manner. Rho kinase protein level was increased by treatment with thrombin. Treatment with the ROCK inhibitor Y27632 attenuated thrombin-mediated MLC phosphorylation without affecting rho kinase protein level. Treatment with the thrombin agonist peptide which acts via the PAR-1 receptor also caused an increase in phospho-MLC levels.

Conclusion: Thrombin activates the ROCK pathway to phosphorylate MLC, likely via the PAR-1 receptor. These results suggest another mechanism by which thrombin may affect BBB integrity through its effects on astrocyte cytoskeletal properties.

Keywords: thrombin, rho kinase, myosin light chain

D7-02

TRAUMATICALLY INJURED ASTROCYTES RELEASE A PROTEOMIC SIGNATURE MODULATED BY STAT3 DEPENDENT CELL SURVIVAL

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Molecular markers associated with CNS injury are of diagnostic interest. Mechanical trauma generates cellular deformation with membrane damage and poration. We used an *in vitro* model of stretch-injury and proteomic analysis to determine protein changes in murine astrocytes and their surrounding fluids. Abrupt pressure-pulse stretching resulted in rapid release of over 75 astrocytic proteins with release profiles reflecting membrane permeability and cell lysis. This acute astrocyte leak-associated ''traumatome'' was overrepresented with metabolic and catabolic proteins compared to their uninjured cellular proteome, bearing implications for post-traumatic metabolic depression. Stretched astrocytes deficient in signal transducer and activator of transcription 3 (STAT3-CKO) released more protein complexes, nuclear proteins, cytoskeletal and transport proteins, consistent with a larger population of lysed cells compared to non-transgenic astrocytes. STAT3-CKO astrocytes also had reduced basal expression of GFAP, lactate dehydrogenase B (LDHB), aldolase C (ALDOC) and astrocytic phosphoprotein 15 (PEA15), and elevated levels of tropomyosin 4 (TPM4) and a-actinin 4 (ACTN4), as well as reduced stretch-injury tolerance and elevated necrosis. Stretching led to cellular depletion of PEA15 and GFAP, and caused GFAP filament disassembly in distinct subpopulations of injured astrocytes that varied between genotypes. PEA15 and ALDOC signals were reduced in injured astrocytes at 6 hours after mouse crush spinal cord injury (SCI) and were elevated in reactive astrocytes 1–3 days post-injury. In contrast, a-crystallin (CRYAB) was elevated in acutely injured astrocytes, and absent from uninjured and reactive astrocytes, demonstrating marker heterogeneity. Together these findings reveal a proteomic signature of traumatically-injured astrocytes reflecting STAT3-dependent cellular survival, with potential diagnostic value.

Keywords: traumatome, proteomic, GFAP, PEA 15, TBI, Biomarker

D8 Poster Session VIII - Group D: Neuroprotection

D8-01

NECK STRENGTH IS ASSOCIATED WITH HISTORY OF CONCUSSION IN AMATEUR ADULT SOCCER PLAYERS

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Cervical musculature is essential for maintenance of posture and stabilizing the head. Greater neck strength (NS) has been associated with reduced risk of concussion in high school athletes. Soccer players are at risk of concussion both from collisions and from heading the ball. Our objective was to assess the association of measures of NS and anthropometric measurements as predictors of risk of concussive injury in soccer players. 57 players (41 men, 16 women, ages 18–51) were drawn from an ongoing longitudinal study of sub-concussive and concussive mild TBI in amateur soccer players. Number of prior concussions was reported by each subject. Subjects underwent NS measurement in isometric extension (EXT), forward flexion (FF), and right (RLF) and left lateral flexion (LLF) using the microFET2 digital dynamometer (Hoggan Scientific) mounted on a custom wall frame. Height, weight, neck length, neck circumference, and head circumference were measured and body mass index (BMI) was computed. Players without a history of concussion ($n=36$) had significantly greater NS in FF than players with a history of concussion ($n=21$) ($p=0.011$). Number of prior concussions was negatively correlated with NS in FF ($p=0.003$) and EXT ($p=0.019$). NS was correlated with weight in all 4 directions ($p<0.05$) and with neck circumference in FF, EXT, and LLF ($p<0.01$). However, neck circumference and weight were not correlated with number of prior concussions. Results were corrected for multiple comparisons using false discovery rate correction (alpha = 0.05). In soccer players increased NS is associated with decreased risk of concussion. Anthropometric measurements are correlated with NS, but not with history of concussion and may not provide a reliable means for risk assessment. Further study is warranted toward developing interventions to mitigate concussion risk.

Keywords: sports-related concussion, mild traumatic brain injury, neck strength, anthropometrics

D8-02

NEUROPROTECTION WITH PEG-HYDROPHILIC CARBON CLUSTERS IN MILD TRAUMATIC BRAIN INJURY COMPLICATED BY HYPOTENSION IN RODENTS

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Introduction: The neurological consequences of traumatic brain injury worsen when the injury is complicated by hypotension. A new class of 2×40 nm carbon nanoparticle antioxidants, poly(ethylene glycol)-functionalized hydrophilic carbon clusters (PEG-HCCs) had been previously shown to rapidly restore cerebral blood flow (CBF) and neutralize reactive oxygen species in a mild cortical impact injury complicated by hypotension (mCCI + HT) model, when administered during resuscitation. The purpose of this research was to study long term neurological outcome following administration of PEG-HCCs in mCCI + HT model.

Methods: Thirty two Long Evans rats, weighing 300–350 grams, were randomly assigned to two groups: saline-treated (n = 16) and PEG-HCC treated (n = 16). All rats were anesthetized with isoflurane and subjected to a mCCI [3 m/sec, 2.5 mm deformation], followed by a hypotensive phase for 50 minutes (mean arterial pressure or MAP < = 40), a prehospital phase for 30 minutes (infusion of Lactate Ringer's until MAP > = 50), and a hospital phase of 30 minutes where the shed blood was reinfused while breathing 100% oxygen. Saline or PEG-HCC (2 mg/kg) were administered IV at the beginning of resuscitation and again two hours after the first injection. Behavioral outcome measures included beam walking and balance tests on days 1–5, and Morris water maze on days 11–15. The rodents were euthanized and histological measures were performed.

Results: Performance during beam walking and balancing were significantly improved in the PEG-HCC treated group when compared to saline-treated groups ($P = 0.007$, $P > 0.001$ respectively). Treatment with PEG-HCC also improved the latency of finding the platform was significantly faster on the first day of Morris water maze when compared to the saline-treated group (Treatment X Day, $P < 0.001$). There was a trend in the differences in contusion volumes ($P = 0.054$).

Conclusions: PEG-HCCs have been shown to restore CBF as well as neutralize dangerous reactive oxygen species. This study demonstrates that PEG-HCCs also improve neurological recovery.

Keywords: Nanoparticles, antioxidants, brain injury, PEG-HCC, hypotension, reactive oxygen species

D8-03

NEUROPROTECTIVE EFFICACY OF ERYTHROPOIETIN-MIMETIC PEPTIDE (ARA290) WITH DELAYED ADMINISTRATION AFTER CORTICAL IMPACT INJURY

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Objectives: ARA290, an erythropoietin-mimetic peptide that does not stimulate erythropoiesis, improved neurological outcome at two weeks following severe cortical impact injury (sCCI) when given in a dose of 30 mg/kg q12h for 3 days starting one hour post-injury. The objective of this study was to determine neuroprotective efficacy of ARA 290, delaying the first dose until 3 hours after injury and with more long-term (30 day) outcome.

Methods: 192 male rats underwent sCCI and were randomly assigned to different IV treatment regimens (continuous infusion, q6h, q12h, or q24h) for 3 days starting at 3 hours post-injury. Primary outcome measure was a composite neurological score of behavioral performance (beam walking and Morris water maze) and histological measures (CA1 cell count). Individual tests were analyzed as secondary outcomes. For q6h and q24h dosing groups, the experiment was subsequently repeated with a more difficult Morris water maze task at four weeks post-injury (reversing platform position with smaller platform).

Results: Composite neurological outcome score was significantly better in the ARA290 treated animals than in the vehicle treated animals (score difference 0.22 ± 0.10, $P = 0.037$). Best composite score occurred with q24h (score difference 0.54 ± 0.21, $P = 0.013$). The effect of drug treatment did not depend on the dosing regimen. The motor tasks were significantly better in the ARA290 group (beam walking test, $p = 0.0003$ and beam balance test, $p = 0.05$). Performance on the Morris water maze task was not improved in the ARA290 treated animals with the standard testing procedure. However, when the study was repeated with the more difficult Morris water maze task, ARA290 treated animals in the q24h dosing regimen group had significantly improved performance.

Conclusions: ARA290 significantly improved long-term neurological recovery when treatment was started at 3 hours post-injury, and continuous infusion of ARA290 did not provide better neuroprotection than the intermittent dosing regimens.

Keywords: Cortical Impact Injury, ERYTHROPOIETIN - MIMETIC PEPTIDE (ARA290)

D8-04

LITHIUM AND VALPROATE ADMINISTRATION PROVIDES NEUROPROTECTION AFTER MILD TRAUMATIC BRAIN INJURY COMPLICATED BY HYPOTENSION

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Introduction: Lithium (Li) and Valproate (VPA) are two antiepileptic drugs that are shown to be neuroprotective, due in part to inhibition of glycogen synthase kinase-3 (GSK-3) and histone deacetylases (HDACs), respectively. The purpose of this research was to study neurological outcomes, following administration of Li-VAP in mild controlled cortical impact (mCCI) injury, complicated by hypotention (HT) in the rodent model.

Methods: A total of 32 Long Evans rats, weighing 300–350 grams, were randomly assigned to two groups: saline-treated (n = 16) and Li + VAP treated (n = 16). All rats were anesthetized with isoflurane and subjected to a mCCI ([3 m/sec, 2.5 mm deformation]), followed by a hypotensive phase for 50 minutes (mean arterial pressure or MAP < = 40), a prehospital phase for 30 minutes (infusion of Lactate Ringer's until MAP > = 50), and a hospital phase of 30 minutes where the shed blood was reinfused while breathing 100% oxygen. Both groups were given q24h x 4 intraperitoneal (IP) injections of either saline or Li (20 mg/kg) + VPA (42 mg/kg), with the first dose administered at the beginning of resuscitation. Behavioral outcome measures included beam walking and beam balancing tests for motor coordination at days 1–5, and Morris water maze (MWM) for spatial navigation days 11–15. After 15 days, animals were euthanized and histological measures were performed.

Results: Performance during beam walking and balancing were significantly improved in the Li-VAP treated group when compared to saline-treated groups ($P = 0.006$, $P = .003$ respectively). Li-VAP administration also significantly improved latency of hidden platform location on the first day of MWM when compared to the saline-treated group (Treatment X Day, $P < 0.001$).

Conclusions: Compromised cerebral blood flow following brain injury due to HT further complicates the outcome and rehabilitation in

a clinical setting. Li and VAP robustly improved neurological recovery when given soon in this model that mimics a ploytraumatic clinical situation.

Keywords: Hypotension, Lithium, Valproate, Mild Traumatic Brain

D8-05

LOWERING TUMOR NECROSIS FACTOR-α SYNTHESIS AMELIORATES NEURONAL AND COGNITIVE LOSS AFTER MILD TRAUMATIC BRAIN INJURY IN MICE

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Treatment of traumatic brain injury (TBI) represents an unmet medical need, as no effective pharmacological treatment currently exists. Development of such a treatment requires a fundamental understanding of the pathophysiological mechanisms that underpin the sequelae resulting from TBI, particularly the ensuing neuronal cell death and cognitive impairments. Tumor necrosis factor-alpha (TNF-a) is a cytokine that is a master regulator of systemic and neuro inflammatory processes. TNF-a levels are reported rapidly elevated post TBI and, potentially, can lead to secondary neuronal damage. To evaluate the role of TNF-a in TBI, particularly as a drug target, the present study evaluated time-dependent TNF-a levels in brain in a mouse closed head 50 g weight-drop mild TBI (mTBI) model in the presence and absence of post-treatment with an experimental TNF-a synthesis inhibitor, 3,6'-dithiothalidomide. Brain TNF-α levels peaked at 12 hr post injury, and returned to baseline by 18 hr. This was accompanied by neuronal loss and an increase in astrocyte number (evaluated by NeuN and GFAP immunostaining respectively), as well as an elevation in the apoptotic death marker BID at 72 hr. Impairments in measures of cognition, evaluated by novel object recognition and passive avoidance paradigms, were evident at 7 days after injury. Treatment with the TNF-α synthesis inhibitor 3,6'-dithiothalidomide 1 hr post injury prevented the mTBI-induced TNF-α elevation and ameliorated the neuronal loss (NeuN), elevations in astrocyte number (GFAP) and BID, and cognitive impairments. Cognitive impairments were prevented by treatment as late as 12 hr post mTBI, but were not reversed when treatment was delayed until 18 hr. These results suggest that pharmacologically limiting the generation of TNF-α post mTBI may mitigate secondary damage and define a time window of up to 12 hr to achieve this reversal.

Keywords: Neuroprotection, Inflammation, Neurodegeneration, Cognition

D8-06

BIODEGRADABLE NEURO-SPINAL SCAFFOLD PRESERVES SPINAL CORD ARCHITECTURE FOLLOWING SPINAL CONTUSION INJURY IN RATS

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Severe spinal cord injury (SCI) is accompanied by disruption of spinal cord architecture, including cystic cavitation and tissue loss. We hypothesized that implantation of a biodegradable, biomaterial scaffold into the injured spinal cord could serve as a locus for appositional healing and tissue remodeling that would preserve spinal cord architecture. We evaluated the effect of implantation of scaffolds composed of a block copolymer of poly(lactic-co-glycolic acid) and poly(L-lysine) (PLGA-PLL) on preservation of spinal architecture in a rat contusion model of severe spinal cord injury (SCI). A spinal T10 contusion injury was created in female Sprague-Dawley rats with a Precision Systems IH Impactor (220 kDyn). Cylindrical scaffolds (1.0 mm diameter, 2.0 mm length) were surgically implanted at the lesion site between 24 and 72 hours later. Body weight, development of mechanical allodynia, and recovery of coordinated hind limb function using the Basso, Beattie, and Bresnahan (BBB) scale were evaluated for 12 weeks. Spinal architecture was evaluated at 12 weeks by morphometric analysis of paraformaldehyde fixed frozen sections (20 μm) stained with hematoxylin & eosin (H&E). Scaffold implantation did not result in mechanical allodynia, did not impair body weight gain, and did not interfere with partial recovery from full hind-limb paralysis. Histological analysis revealed that rats in the non-treated control group developed large cavities surrounded by a rim of spared tissue. In contrast, in rats treated with scaffold implantation surgery, cavity volume decreased by 86% and spared tissue width increased by 44%. Although scaffolds were fully resorbed by 12 weeks after implantation, the amount of remodeled tissue at the site of implantation in the lesion epicenter increased by 111%. These results demonstrate that PLGA-PLL scaffold implantation in the acutely injured spinal cord can reduce cavitation, promote tissue sparing and remodeling, and act as a locus for appositional healing. Scaffold implantation preserves spinal cord architecture and may play an important role in combinatorial spinal cord repair strategies.

Keywords: biomaterial, tissue engineering, scaffold, implantation, biodegradable

D8-07

HYPERTONIC SALINE THERAPY AND DECOMPRESSIVE SURGERY WITH MULTI-MODAL THERAPY IN ACUTE SPINAL CORD INJURY

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Acute spinal cord injury is a debilitating condition that has significant associated morbidity and mortality that has progressed to becoming a chronic medical condition with an estimated prevalence of about 270,000 individuals and with an incidence of 12,000 new cases each year in the United States. The majority of spinal cord injury cases are secondary to trauma and permanent neurological deficits are believed to be due to secondary injury most significantly due to compressive forces and edema. Despite advances in intensive care and refinement of surgical approaches, there are currently no widely accepted medical or surgical interventions for managing spinal cord edema. Interestingly, however, there has been generally more literature and data on decreasing cerebral edema, including the administration of hypertonic saline. There have been several basic science articles written on the proposed efficacy of hypertonic saline administration in decreasing spinal cord edema after acute spinal cord injury but no known clinical studies to date. A review of the

literature has yielded different treatment modalities in acute spinal cord injury with mixed results including surgical decompression and neuroprotection methods but none evaluating the efficacy of hypertonic saline administration. After a recent case of a young adult male who presented with acute spinal cord injury at our institution, neuroprotective methods and decompressive surgery were used in addition to the administration of hypertonic saline with elevated sodium goals. The patient's discharge neurological function improved with this multi-modal therapy and this is the first known case in the English language literature in which hypertonic saline was used in the treatment of acute spinal cord edema. Therefore, we hereby provide a review of this case and the current literature addressing spinal cord edema in the setting of acute spinal cord injury and the implications on neurological recovery.

Keywords: spinal cord injury, hypertonical saline, decompressive surgery, multi-modal therapy, spinal cord edema

D8-08

PROTECTIVE EFFECT OF N-ACETYLCYSTEINE AMIDE (NACA) AGAINST BRAIN DAMAGE AFTER EXPOSURE TO BLAST IN A RAT MODEL

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Blast-induced traumatic brain injury (bTBI) has been a leading cause of neurocognitive and psychological impairment in the military population. Brain edema and Blood Brain Barrier (BBB) function are compromised in TBI including blast. In this study we determined if blast induced changes in intracranial pressure (ICP), and BBB breakdown, could be ameliorated by administration of the antioxidant N-acetylcysteine amide (NACA).

Rats were exposed to either single or three blast overpressures (BOP) (110 kPa) with animal's head facing the blast wave. NACA was administered either pre- or post-blast by single i.p injection (500 mg/kg). ICP was monitored by a telemetric device over a period of 7 days. BBB permeability and integrity were determined by Evans Blue (EB) staining and occludin immunoreactivity, respectively.

EB leakage into the brain was increased brain two hours after single or multiple exposures of blast, indicating a compromise in the integrity and function of the BBB. Concomitantly, a significant elevation in ICP was observed after single or repetitive exposures to BOP. In the single-blast group, ICP immediately returned to near pre-blast levels after post-blast NACA administration. Also, in the repetitive-blast group there was a significant amelioration in the ICP increase by NACA. Immunoreactivity of occludin, a component of tight junctions in BBB was significantly decreased after exposure to blast and this was prevented by NACA administration. The protective effect of NACA against blast-induced changes could be related to its antioxidative effect as demonstrated by suppression of nitrotyrosine immunoreactivity increase after blast.

These results demonstrate that BBB breakdown may be an important factor in the mechanism of bTBI. The subsequent ICP increase can be used as one of the markers of brain damage and the antioxidant NACA may be useful as a new therapeutic modality for ameliorating BOP-induced brain damage.

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Keywords: Blast Brain Injury, N-acetyl cysteineamide, Antioxidant

D8-09

THE EFFECT OF INTERNAL JUGULAR VEIN COMPRESSION ON HEMORRHAGE IN A PORCINE CONTROLLED CORTICAL INJURY MODEL

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Internal jugular vein (IJV) compression reduced axonal injury in a rat model of traumatic brain injury (TBI). However, IJV compression also increases cerebral perfusion pressure. If this increases hemorrhage after TBI, the overall impact of IJV compression might become harmful. We tested the hypothesis that IJV compression increases hemorrhage after TBI in a porcine controlled cortical impact (CCI) model.

Methods: Yorkshire swine were anesthetized and prepared for surgery with respiratory support, analgesia and vital signs monitoring. An 18 mm wide burr hole was created over the right cortex. An Integra Camino pressure sensor was placed in the left cortex. In IJV compression animals, a custom-made collar was used to compress the IJV until intracranial pressure rose by 1 mmHg. A beveled, cylindrical indenter 15 mm in diameter was used with a Leica ImpactOne CCI device to injure the exposed cortex (velocity = 3.5 m/s; depth = 9 mm; dwell = 400 ms). The collar was removed immediately after injury and the burr hole was filled with bone wax. The animal was euthanized 5 hours later. The brain was fixed and sections were obtained from 10 predefined locations in the cortex of each animal. A blinded, clinical neuropathologist assigned a score between 0 and 2 to the level of subarachnoid hemorrhage (SAH) in each section. Scores for all 10 sections were totaled to measure the overall level of SAH in each animal.

Results: 4 pigs were injured, 2 with IJV compression and 2 without (controls). SAH levels were 3.5 and 4.5 in the IJV compression animals and 9.5 and 10.25 in the control animals.

Conclusions: Definitive conclusions cannot be drawn due to the small sample size. In the animals tested, IJV compression did not increase hemorrhage as hypothesized. In fact, it reduced hemorrhage.

This study was sponsored by Q30 Sports Science, LLC.

Keywords: protective device, hemorrhage, porcine, controlled cortical impact

D8-10

THE EFFICACY OF PROGESTERONE DEPENDS ON THE TRAUMATIC BRAIN INJURY MODEL

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Progesterone was previously reported to improve outcomes in preclinical studies of traumatic brain injury. Recent phase 3 clinical trials, however, reported no clinical benefit of progesterone treatment for moderate-to-severe as well as severe traumatic brain injuries. Given the heterogeneity in human traumatic brain injuries, we aimed to reassess the effectiveness of progesterone treatment in two preclinical traumatic brain injury models. We compared progesterone treatment (16 mg/kg for 5 days) in mechanically identical controlled cortical impacts to the medial frontal cortex and the parasagittal cortex in rats. During the first week following injury, progesterone improved motor performance on the beam balance in both injury models. In the Morris water maze test, progesterone improved learning and memory only in

animals that had received impacts to the medial frontal cortex and not in the parasagittal injury model. In the elevated plus maze, lesions to the medial frontal cortex increased the time the rats spent in the open arms which may indicate decreased anxiety and greater risk-taking behavior. This behavior was not attenuated by progesterone. The increase in the open arm time was modest in parasagittal injuries. Nonetheless, progesterone attenuated this modest increase back to levels similar to that of sham surgical controls. These data illustrate that the efficacy of post-traumatic progesterone treatment may depend on the brain region injured. Hence, the clinical translation of progesterone might benefit from additional stratification of patients accounting for the position of the brain lesions.

Keywords: progesterone, controlled cortical impact, medial frontal cortex, parasagittal cortex, neurobehavior

D8-11

TBI-INDUCED METABOLOMIC PROFILES IN ENERGETIC, OXIDATIVE STRESS AND INFLAMMATORY PATHWAYS ARE IMPROVED BY ETHYL PYRUVATE TREATMENT

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This study examined metabolomic changes after traumatic brain injury (TBI) and ethyl pyruvate (EP) treatments. Adult male Sprague-Dawley rats were injected (IP) with EP (40 mg/kg) or vehicle (Veh; 0.1M PBS) at 0, 1, 3 and 6 h after sham injury (n = 6/group) or TBI (contusion; n = 9/group) to the left parietal cortex. At 24 h post-injury left cortical tissue was harvested and frozen samples were processed for global metabolic profiles using ultrahigh performance liquid chromatography-tandem mass spectroscopy (UPLC-MS/MS) or gas chromatography-MS at Metabolon, Inc. (Durham, NC). Two-way ANOVA on the dataset of 503 identified biochemicals revealed significant ($p's < 0.05$) main effects of Injury for 364 compounds, of Drug for 19 compounds and a significant interaction for 56 biochemicals. ANOVA contrasts (TBI-Veh vs. Sham-Veh) indicated 220 biochemicals increased after TBI and 98 were decreased by injury. In TBI-EP vs. TBI-Veh comparisons, 48 biochemicals were increased and 13 were decreased by the EP treatments. Principle component analysis showed Sham-injured rats formed an overlapping population, while TBI-Veh and TBI-EP generated two separate but partially overlapping populations. Random forest yielded a predictive accuracy of 77% for group classifications (random segregation would yield a predictive accuracy of 25%). The top 30 metabolites separating treatment groups indicated key differences in carbohydrate metabolism, amino acid metabolism, lipid metabolism and peptides after TBI and/or EP treatments. Overall, the results indicated significant TBI-induced alterations in pathways related to energetics, oxidative stress and inflammation. Glycolytic function was decreased, with increased use of branched-chain amino acids and fatty acid beta-oxidation for energy production after TBI. Glycogen synthesis was decreased, with an increase in glycogenolysis and increased glucose levels post-TBI. EP treatment after TBI increased acetyl CoA and decreased glycogenolysis, consistent with EP use in the TCA cycle and decreased energy demand. More subtle changes in TBI-EP rats were consistent with an anti-oxidant and anti-inflammatory function for EP.

Support: UCLA Brain Injury Research Center, P01NS058489 and SUMITOMO Life Social Welfare Services Foundation.

Keywords: bioenergetics, controlled cortical impact, cerebral cortex, inflammation, metabolomics, oxidative stress

D8-12

SELENIUM DEFICIENCY IS DETRIMENTAL TO MITOCHONDRIAL RESPIRATION FOLLOWING TRAUMATIC BRAIN INJURY

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Traumatic brain injury continues to be a substantial clinical problem with few available treatment strategies. Individuals who are at a greater risk for sustaining a brain injury, such as professional athletes and military personnel, may benefit from a prophylactic supplement that would intervene in the neurodegenerative pathways immediately following injury. Different dietary levels of selenium, a cofactor for antioxidant enzymes, were supplemented in the diets of male Sprague-Dawley rats. Included in this study were diets deficient in selenium, equivalent levels to normal rat chow, and two levels of enriched selenium. Animals received diets for 4 weeks prior to receiving a severe (2.2 mm) controlled cortical impact brain injury or sham craniotomy. Naïve animals maintained on these diets showed a decrease or increase in central nervous system tissue levels relative to the amount of selenium present in the diet. Twenty-four hours following impact, a cortical punch directly surrounding the injury epicenter was isolated for mitochondrial respiration assays. Respiration was measured using oxygen consumption rates (Seahorse Bioscience©) in response to mitochondrial substrates, mimicking various stages of the electron transport chain. These studies showed that selenium deficiency is detrimental to mitochondrial respiration and exacerbated the observed injury effect. This effect was seen in State III, State V (complex I), and State V (complex II) driven respiration, as measured through injection with endogenous substrates pyruvate/malate and ADP, FCCP, and rotenone and succinate, respectively. Additionally, animals on the selenium deficient diet had a decrease in glutathione peroxidase activation following injury. Animals given diets enriched in selenium did not show significant improvements over animals receiving control diets, suggesting a possible ceiling effect with selenium supplementation. The exacerbated injury outcomes with selenium deficiency suggests that there are critical levels of dietary selenium for maintenance of mitochondrial function following injury. Supplementation with selenium above normal dietary levels, however, may not enhance protection of mitochondria after TBI.

Keywords: Mitochondria

D8-13

INSULIN-LIKE GROWTH FACTOR-1 OVEREXPRESSION PROMOTES SURVIVAL OF ADULT-BORN NEURONS AFTER TRAUMATIC BRAIN INJURY

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The pathology associated with traumatic brain injury (TBI) manifests in motor and cognitive dysfunction following injury. Immature neurons residing in the neurogenic niche of the dentate gyrus (DG) in the hippocampus, a brain structure required for learning and memory, are particularly vulnerable to TBI. The inability to restore this population of hippocampal immature neurons following TBI has been causally

linked to cognitive impairment. Insulin-like growth factor-1 (IGF1) is a potent neurotrophic factor capable of mediating neuroprotective and neuroreparative processes. We have shown that elevating brain levels of IGF1 stimulates hippocampal neurogenesis, enhancing the recovery of immature neuron numbers after severe TBI in mice. However, little is known about the effectiveness of IGF1 to promote long-term survival of neurons born after injury. To this end, astrocyte-specific IGF1 conditionally overexpressing mice (IGF1-TG) and wild-type (WT) mice received controlled cortical impact or sham injury and 50 mg/kg BrdU (i.p.) twice daily for 7 days following TBI. At six weeks following injury, total numbers of proliferated cells ($BrdU^+$) and the subset expressing a mature neuronal marker ($NeuN^+/BrdU^+$) were counted at the injury epicenter. IGF1 significantly increased $NeuN^+/BrdU^+$ cell density at 6 weeks post-injury ($p < 0.05$, compared to WT injured mice). These data suggest that IGF1 stimulates the formation of new hippocampal neurons acutely after brain injury and that these new neurons survive to maturity. Future studies will examine the electrophysiological function of these newborn neurons.

Keywords: Neurogenesis, Survival, IGF1

D8-14

SYNERGISTIC EFFECTS OF β-HYDROXYBUTYRATE AND ACETYL-L-CARNITINE ON MITOCHONDRIAL FUNCTION AFTER SPINAL CORD INJURY

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Mitochondrial dysfunction and oxidative stress are key factors after contusion spinal cord injury (SCI) that lead to cell death and ultimately functional deficits and, therefore, serve as pivotal targets for SCI therapeutics. The current study evaluated the effects of administering ketone bodies, namely β-hydroxybutyrate (BHB) on mitochondrial function and oxidative stress following SCI. Moreover, we tested BHB treatment either alone or delivered in combination with acetyl-l-carnitine (ALC), an alternative bio-fuel for mitochondria. Injured Sprague-Dawley rats (250 kdyn at L1/L2 spinal level) were divided into 3 treatment groups (n = 6/group): 1) Vehicle-treated-injured, 2) 1.66 mmol/kg BHB-treated injured and 3) 1.66 mmol/kg BHB + 300 mg/kg ALC-treated injured. Drugs were administered intraperitoneally at 1 hr post-injury followed by insertion of an osmotic mini-pump (s.c.) to deliver Vehicle or BHB (1.66 mmols/kg/day) or BHB + ALC (300 mg/kg/day) for 24 hrs. A Sham group received only a T12 laminectomy. At 24 hr post-injury, spinal cord mitochondria were isolated and assessed for oxygen consumption rate (OCR) using Seahorse Bioscience XFe24 extracellular flux analyser, as well as for content of endogenous antioxidant glutathione (GSH). Results showed significantly ($p < 0.05$) decreased OCR (~50%) in Vehicle-treated injured group compared to Shams and that treatment with BHB alone significantly ($p < 0.05$) preserved mitochondrial OCR (~35% lower than Sham) after 24 hrs. Furthermore, combined treatment with BHB + ALC additively restored mitochondrial OCR (~10% lower than Sham) compared to BHB alone. Notably, while SCI also resulted in significant ($p < 0.05$) depletion of GSH (~25%), continuous treatment with BHB completely restored GSH to normal levels. Ongoing experiments are assessing whether combined BHB + ALC additively normalize oxidative stress parameters and activities of key mitochondrial enzyme complexes at 24 hr post-injury. Planned experiments will assess the effects of such combinatorial treatments on tissue sparing and recovery of hindlimb function following SCI.

Keywords: mitochondrial respiration, functional recovery, glutathione, oxidative stress

D8-15

RE-PURPOSING AN FDA-APPROVED DRUG AS AN ANTIOXIDANT TO SCAVENGE REACTIVE CARBONYLS FOLLOWING TBI-INDUCED LIPID PEROXIDATION

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Lipid peroxidation is a key contributor to the pathology of traumatic brain injury (TBI). Traditional antioxidant therapies are intended to scavenge the free radicals responsible for either the initiation or propagation of lipid peroxidation (LP). However, targeting free radicals after TBI is difficult as they rapidly react with other cellular macromolecules. Our laboratory utilizes a novel antioxidant approach that scavenges the final stages of LP i.e., the formation of carbonyl-containing breakdown products. By scavenging breakdown products such as the highly reactive and neurotoxic aldehydes 4-hydroxynonenal (4-HNE) and acrolein, we are able to prevent the covalent modification of cellular proteins. Without intervention, carbonyl additions render cellular proteins nonfunctional which initiates the loss of ionic homeostasis, mitochondrial failure, and subsequent neuronal death. Phenelzine (PZ) is an FDA-approved monoamine oxidase inhibitor traditionally used for the treatment of depression. However, PZ also possesses a hydrazine functional group capable of covalently binding carbonyls. We hypothesized that PZ will protect mitochondrial function and reduce markers of oxidative damage by scavenging reactive aldehydes. Indeed, in our *ex vivo* experiments the exogenous application of 4-HNE or acrolein significantly reduced respiratory function and increased markers of oxidative damage ($p < 0.05$) in isolated non-injured rat cortical mitochondria, whereas PZ pre-treatment significantly prevented mitochondrial dysfunction and oxidative damage in a concentration-related manner ($p < 0.05$). We attribute PZ's neuroprotective effects to the hydrazine moiety based on experiments demonstrating that a structurally similar MAO inhibitor, pargyline, that lacks the hydrazine moiety was unable to protect mitochondria. Our *in vivo* experiments demonstrated that PZ treatment, 10 mg/kg s.c. begun at 15 minutes and repeated q12 hrs, significantly attenuated mitochondrial respiratory failure 72 hours post-injury following rat controlled cortical impact injury, while also significantly reducing cortical lesion volume 2 weeks post-injury. We are presently investigating the optimal PZ dosing regimen for improvement of cognitive and motor behavioral recovery and the therapeutic window for the neuroprotective effects of the drug to determine its feasibility for translation into human TBI testing.

Keywords: Phenelzine, Mitochondria, Oxidative Damage, 4-HNE, acrolein, TBI

D8-16

BIOMARKER PROFILES SUPPORT A NEUROPROTECTIVE EFFECT OF LEVETIRACETAM IN TBI: FINDINGS FROM OPERATION BRAIN TRAUMA THERAPY

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Levetiracetam (LEV) is a new anti-epileptic used for prevention of post-traumatic epilepsy that has been shown to be neuroprotective and improve outcomes after TBI even in the absence of seizure activity. The present work, part of the Operation Brain Trauma Therapy (OBTT) a multi-center pre-clinical drug screening consortium, investigated the effects of early, single-dose LEV treatment on behavioral and histopathological outcomes and TBI biomarkers across multiple models.

Adult rats subjected to controlled cortical impact (CCI), fluid percussion (FPI), or penetrating ballistic-like brain injury (PBBI) received a single 15 min post-injury IV dose of LEV (54 or 170 mg/kg) or vehicle. Circulating concentrations of glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase (UCH-L1) were measured by ELISA at 4 and 24h after-injury.

In CCI, LEV 170 mg/kg was able to markedly improve motor functions and reduces hemispheric tissue loss ($p < 0.05$ vs vehicle). These effects were accompanied by a significant reduction in GFAP concentration at 24h ($p < 0.05$ vs vehicle). A positive, albeit modest, effect on motor and cognitive functions was noted in animals treated with LEV 54 mg/kg. In FPI, LEV at both doses trended towards improved cognitive outcomes in several behavioral paradigms, but with no effect on biomarker levels. In PBBI, there was no motor or cognitive benefit from either dose and no benefit on histology. In the LEV 54 mg/kg group, GFAP levels returned to sham levels at 24h after-injury. LEV had no effect on UCH-L1 concentrations.

Our results suggest a potential application of early, single-dose Levetiracetam as a neuroprotective therapy for specific types of TBI. Furthermore, GFAP can be used to identify and monitor drug effect and might be a valuable theragnostic marker. Support:US Army W81XWH-10-1-0623.

Keywords: Glial fibrillary acidic protein, Ubiquitin carboxyl-terminal hydrolase-L1, Fluid percussion injury, Controlled cortical impact, Penetrating ballistic-like brain injury, Rat

D8-17

EVALUATION OF GLIBENCLAMIDE IN THE MIAMI FLUID PERCUSSION MODEL OF TRAUMATIC BRAIN INJURY: AN OBTT CONSORTIUM STUDY

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Glibenclamide (GLI) is a sulfonylurea receptor (SUR1) regulated $NC_{Ca\text{-}ATP}$ channel antagonist that has shown promise in preclinical traumatic brain injury (TBI) studies. Male Sprague-Dawley rats were anesthetized and underwent moderate fluid percussion (FPI; 1.8–2.1 atm) TBI. Rats were randomized into three groups and administered GLI (10 μg/kg IP) or vehicle 10 min post-TBI followed by SQ Alzet mini pump implantation (1.0 μl/h) for drug or vehicle administration. The pump was removed between 168 and 172 hrs post-injury. Animal groups were TBI-GLI (n = 15), TBI-Veh (n = 15) or Sham (n = 15). Rats were tested on day 7 post-injury for sensorimotor function (gridwalk, cylinder task). On days 13–21, rats were assessed for cognitive function utilizing the simple place task, probe trial and working memory task. On day 21, brain tissue was processed for histology. One-way ANOVA was significant for the cylinder task ($p < 0.05$) but not for the gridwalk. TBI-GLI animals were significantly improved compared to TBI-Veh ($p < 0.05$). For the hidden platform task, two-way repeated measures ANOVA for latency was not significant for group x day. TBI GLI treated animals treated groups exhibited similar latencies to TBI-Veh. Repeated measures ANOVA for working memory latency was significant for trial ($p < 0.001$), but not group or group x trial. Lesion volume or cortical volume loss was not significant between the TBI groups. We conclude that sustained treatment with GLI after FP produced a mild motor benefit but did not improve cognitive function or decrease histological damage. Although this drug does target several pathomechanisms including edema and necrosis, the current study reports only motor benefit for GLI treatment in the rat FPI model. Our behavioral findings mirror the motor benefit seen in CCI, although lack of cognitive benefit dampens enthusiasm. Support: US Army W81XWH-10-1-0623.

Keywords: Glibenclamide, OBTT, fluid percussion

D8-18

EVALUATION OF GLIBENCLAMIDE IN THE PITTSBURGH CONTROLLED CORTICAL IMPACT MODEL OF TRAUMATIC BRAIN INJURY: AN OBTT CONSORTIUM STUDY

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Preclinical studies suggest that Glibenclamide (GLI) improve outcomes in TBI through decreasing cerebral edema. GLI (FDA approved) inhibits the sulfonylurea receptor SUR1. SUR1 also associates with Trpm4 and mediates cerebral edema via water influx. Thus, Operation Brain Trauma Therapy (OBTT) selected GLI for evaluation. In Pittsburgh we studied the effect of GLI on motor, cognitive and neuropathological outcomes in CCI. Adult, male, Sprague-Dawley rats were divided into 3 groups (n = 10/group): sham, CCI + vehicle, CCI + GLI. Anesthetized rats underwent CCI vs sham. An intraperitoneal loading dose (10 μg/kg) was given 10 min post injury, followed by a 7-d subcutaneous-infusion at 0.2 μg/h. Beam balance (BB) and walking (BW) were assessed at d1-5. Cognitive outcomes were assessed using Morris Water Maze (MWM, 14-20d). Contusion volume and hemispheric tissue loss were assessed on d21. Studies in sham rats estimated that average peak (1h) and steady state concentrations (24h) post-loading dose were 5.4 ± 1.4 and 1.2 ± 0.3 ng/mL, respectively (n = 5). There was benefit on BB and BW in GLI vs vehicle ($p < 0.05$) resulting in full points for treatment for both tasks. Cognitive outcome did not differ between GLI and vehicle groups, and in fact, an intermediate detrimental effect was seen on MWM performance with GLI treatment. Consistent with the motor effect, GLI reduced lesion volume vs vehicle ($p < 0.05$). We conclude, GLI improved motor and histological outcomes after CCI in rats within the rigors of OBTT. GLI is the only drug thus far tested in OBTT to reduce contusion volume in CCI, but lack of cognitive benefit is disappointing. Given that it targets brain edema, its effects in CCI may be underestimated by the craniectomy. Further studies are warranted in contusion. Support:USArmyW81XWH-10-1-0623

Keywords: Glibenclamide, traumatic brain injury, cognitive and motor outcomes, neuropathologic outcomes, controlled cortical impact

D8-19

EVALUATION OF KOLLIDON VA-64 IN THE CONTROLLED CORTICAL IMPACT MODEL OF TRAUMATIC BRAIN INJURY: AN OBTT CONSORTIUM STUDY

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Introduction: Kollidon VA-64 is an excipient which reduces cellular degeneration, edema, blood-brain-barrier damage, and motor deficits after experimental TBI. We tested a single 15 min post-injury intravenous infusion of VA-64 on neurobehavioral and histopathological outcomes after CCI.

Methods: 40 adult male Sprague Dawley rats were prepared for CCI (4 m/sec, 2.7 mm deformation) or sham. Rats were randomized into four groups: CCI + vehicle, CCI + low-dose VA-64, CCI + high-dose VA-64, and Sham. Treatment was administered intravenously over 5 min starting 15 min post-injury. Functional outcomes were tested via Beam Balance Task (BBT) (days 1–5), Morris water maze (MWM) acquisition (days 14–18) and probe trial (day 18). Rats were sacrificed on day 21 for brain tissue volume analysis.

Results: Groups differed on BBT performance ($p = 0.004$); post hoc testing revealed sham animals balanced longer than vehicle ($p = 0.021$) and high-dose ($p = 0.004$) rats but not low-dose rats ($p = 0.190$). MWM acquisition latency differed by group ($p = 0.004$); post hoc testing revealed longer latencies (vs. sham) in the CCI + vehicle ($p = 0.015$) and CCI + high-dose group ($p = 0.004$) but not CCI + low-dose group ($p = 0.104$). No group differences existed on probe trial. There was no treatment effect of Kollidon VA-64 vs. vehicle on BBT or MWM. Lesion volume and hemispheric volume loss were unaffected by treatment.

Conclusions: Administration of low-dose Kollidon VA-64 produced intermediate benefit on BBT and MWM in the CCI model within the rigors of our OBTT assessment paradigm. Low-dose Kollidon VA-64 may merit additional study in CCI depending on the pending biomarker assessments; however, overall effects were modest.

Acknowledgments
United States Army (W81XWH-10-1-0623).
Keywords: traumatic brain injury, neuroprotection, consortium, rat

D8-20

TAU OLIGOMER SPECIFIC MONOCLONAL ANTIBODY TO TREAT TRAUMATIC BRAIN INJURY

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Introduction: Traumatic brain injury (TBI) causes nearly $50 billion in medical expenses and lost productivity annually, making TBI one of the major health care problems in the United States. TBI can also predispose individuals to develop a pathologically distinct form of tauopathy-related dementia at an early age. We gave a single dose of anti-tau oligomer specific monoclonal antibodies (TOMA) after TBI in rats and examined neuronal injury and vascular reactivity. TOMA is unique in that it only recognizes oligomeric tau, a toxic form of the microtubule protein tau, while leaving normal, functional tau protein intact.

Methods: Male Sprague-Dawley rats were anesthetized, intubated, mechanically ventilated and prepared for fluid percussion injury (FPI). Animals were randomly assigned to receive moderate (2.0 atm) FPI with vehicle (Veh; $n = 6$) or moderate FPI with TOMA (TOMA; $n = 6$). Return of righting reflex (RR) time measurements commenced immediately upon injury. Animals were reanesthetized and 1 hour post FPI they were given either vehicle or TOMA through an intracerebroventricular (icv) injection. Animals survived for 24 hours prior to being euthanized and their brains and middle cerebral arteries (MCA) were collected. We sectioned (coronal, 10 μm thickness) and stained each brain with .001% Fluorojade-C (FJ), and blindly counted FJ-positive cells in the CA1/2 and CA3 regions of the hippocampus. We measured MCA diameter and vascular reactivity, blinded to the treatment group.

Results: We saw a statistically significant decrease (vs. Veh) in the number of FJ + neurons in the TOMA-treated animals, suggesting a possible therapeutic effect. We conclude from these data that TOMA appears to have a beneficial effect on TBI animals, most likely by binding to the toxic tau oligomers that accumulate after FPI.

These studies were completed as part of an interdisciplinary research team funded by The Moody Project for Translational Traumatic Brain Injury Research.
Keywords: tau, therapeutic, antibody, fluid percussion injury

D8-21

THERAPEUTIC APPLICATION OF A PULSED LASER SYSTEM FOR BRAIN TRAUMA

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Background: We have developed a novel, non-invasive short-pulsed laser system for the treatment of traumatic brain injury (TBI). Our proprietary system combines both the benefits of near infrared laser light (808 nm) and of ultrasound waves, which are generated with each short (10 ns) high-energy (5 mJ) laser pulse within the tissue.

Methods: Anesthetized, adult male Sprague-Dawley rats were subjected to moderate blast-induced neurotrauma (BINT) using the Vandenberg device. **S**hort **P**ulsed **L**aser **T**herapy (**SPLT**) was applied transcranially 1 hour after BINT for 5 minutes. Comparisons were performed between SPL-treated rats, rats subjected to BINT but not treated and SHAM controls (rats anesthetized for the same amount of time as the injured rats but not subjected to BINT). Vestibulomotor function was assessed on post-injury days (PID) 1–3 on the beam balance and beam walking tasks. Cognitive function was assessed on PID 6–10 using a working memory water maze test. BDNF and

caspase-3 mRNA expression was measured by qRT-PCR in laser-captured cortical neurons. Microglia activation and neuronal injury was assessed in brain sections by immunofluorescence using specific antibodies against CD11b and activated caspase-3 respectively.

Results: In the vestibulomotor and cognitive tests, SPL-treated animals performed significantly better than the BINT group and similarly to SHAM animals (one-way ANOVA, $P < 0.05$). SPLT up-regulated mRNA encoding BDNF and down-regulated the pro-apoptotic protein caspase-3 in cortical neurons (one-way ANOVA, $P < 0.05$). Immunofluorescence demonstrated that SPLT inhibited microglia activation and reduced the number of cortical neurons expressing the activated form of caspase-3 (one-way ANOVA, $P < 0.05$).

Conclusions: These data strongly support the neuroprotective effect of SPLT and it prompts further studies aimed at developing SPLT as a therapeutic intervention after TBI.

Support: These studies were completed as part of an interdisciplinary research team funded by The Moody Project for Translational Traumatic Brain Injury.

Keywords: Pulsed Laser Therapy, Neurotrauma, Ultrasound, Traumatic Brain Injury

D8-22

FUNCTIONAL PRESERVATION OF RETINAL GANGLION CELLS WITH P7C3-S243 FOLLOWING BLAST MEDIATED TBI

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Traumatic brain injury (TBI) frequently leads to chronic visual dysfunction. The goal of this study was to evaluate potential neuroprotection of retinal ganglion cell (RGC) function by the neuroprotective molecule P7C3-S243 after blast-mediated TBI. Blast-mediated TBI was modeled using an enclosed blast chamber to generate a blast wave. Analysis of RGC function was performed using the neutral position and provocative pattern electroretinogram (PERG) 1, 4 and 16 weeks post injury. Decrements in neutral position PERG after blast-mediated TBI occur in a temporally bimodal fashion, with a temporary recovery 4 weeks after injury followed by chronically persistent dysfunction 16 weeks following induction of injury. However, analysis of the provocative PERG demonstrated a decreased amplitude 4 weeks post injury. Taken together these results indicates persistent sub-clinical RGC dysfunction. We have also shown that treatment with P7C3-S243 prevented a decrease in the provocative PERG 4 weeks post injury. Chronic treatment with P7C3-S243 also prevented chronic changes in the PERG 16 weeks post injury. These results suggest that provocative PERG testing may serve as a noninvasive test in the living organism to identify early damage to the visual system, and may also reflect corresponding damage in the brain that is not otherwise easily detectable. These findings might provide the basis for developing an earlier diagnostic test to identify patients at risk for developing chronic visual dysfunction after TBI at an earlier stage when treatments may be more effective in preventing chronic dysfunction. In addition, we have shown tht treatment with the neuroprotective agent P7C3-S243 after TBI protects the visual system dysfunction after TBI.

Keywords: Retina, Vision, Ganglion Cell, electroretinography

D8-23

EVALUATION OF KOLLIDON VA64 IN THE WRAIR PBBI MODEL: STUDIES FROM THE OPERATION BRAIN TRAUMA THERAPY (OBTT) CONSORTIUM

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Operation Brain Trauma Therapy (OBTT) is a multi-center consortium established to provide cross-model preclinical screening of emerging traumatic brain injury (TBI) therapies. Kollidon VA64, the 7th drug selected for testing by the OBTT, is a novel agent that has demonstrated cell membrane-resealing properties that decrease TBI induced blood brain barrier permeability as well as cytotoxic and traumatic brain edema in both *in-vitro* and *in-vivo* TBI models. Using the standard OBTT protocol, we assessed therapeutic efficacy of Kollidon VA64 on neurobehavioral and neuropathological outcomes in the WRAIR PBBI model of severe TBI. Unilateral frontal PBBI was produced in the right hemisphere of isoflurane anesthetized rats (10% injury severity level). Low (0.2 g/5 mL) or high (0.4 g/5 mL) doses of VA64 were administered as a single intravenous (IV) infusion 15 m post-injury. Motor and cognitive testing was conducted using the rotarod at 7 and 10 days, and Morris water maze (MWM) from 13–17 days post-PBBI, respectively. Rotarod testing revealed similar deficits across all injury groups with mean latencies reduced by $51 \pm 7\%$ (vehicle), $46 \pm 9\%$ (low), and $48 \pm 9\%$ (high) vs. sham; however no significant improvement in motor outcome was detected across animals treated with VA64. MWM results revealed significant deficits in all injury groups with the average latency to find the hidden platform (across testing days) increased by $85 \pm 16\%$ (vehicle), $123 \pm 21\%$ (low), and $106 \pm 18\%$ (high) vs. sham. Although no significant therapeutic effect was detected on spatial learning for MWM acquisition trials, intermediate beneficial effects were observed on the probe (missing platform) trials and thigmotaxis testing where animals treated with the high dose *did not* differ from sham. Overall, the results of the current study indicate that a single post-injury infusion of VA64 conferred only very modest cognitive benefit in the PBBI model. Histology and biomarker results are pending. Supported by U.S. Army Grant W81XWH-10-1-0623.

Keywords: traumatic brain injury (TBI), Kollidon VA64, Operation Brain Trauma Therapy (OBTT), neurobehavior motor cognitive

D8-24

THE EFFECTS OF SLEEP-ALTERING DRUGS ON SLEEP ARCHITECTURE RELATIVE TO TRAUMATIC BRAIN INJURY IN RATS

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Service members often rely on sleep-altering drugs (caffeine/zolpidem) to counteract the effects of sleep-loss and/or insomnia. However, their impact on traumatic brain injury (TBI) recovery is unknown. This study aimed to (1) determine the effects of caffeine/zolpidem on

sleep architecture and (2) identify the extent to which severe penetrating TBI alters sleep homeostasis. Aim_1: Naïve rats were dosed with oral caffeine or zolpidem and Aim_2: Animals were subjected to 10% unilateral, frontal penetrating ballistic-like brain injury (PBBI). Continuous EEG recordings were initiated immediately following drug administration or PBBI surgery.

Caffeine produced significant reductions in total sleep with concomitant increases in wakefulness. All stages of sleep-wake activity were significantly altered; the majority of changes were measured immediately and sustained for 4h. Zolpidem produced significant reductions in wakefulness and increases in slow wave sleep (SWS). Zolpidem reduced rapid eye movement (REM) sleep during the initial 12h, with residual suppression effects evident 24h later. Lastly, PBBI produced rapid reductions in total wakefulness and REM sleep with increases in SWS. PBBI-injured rats showed delayed REM onset, fewer sleep-stage transitions and increased sleep disruptions. These abnormalities persisted through the initial wake and subsequent sleep cycles. Notably, PBBI-injured rats displayed bioelectrical discordance with injury-induced alterations in REM and SWS sleep more prominent/persistent within the injured hemisphere.

Overall, these results demonstrate 1) that drugs routinely used during deployment can significantly alter the sleep signature and 2) alterations in baseline patterns of sleep disturbances in the PBBI model. Notably, disruption in REM sleep, which was most prominent following severe TBI, is also associated with decreases in memory consolidation, reduced reaction reflexes and increased mental health comorbidities. Further studies are needed to determine the extent drug-induced reductions in REM sleep may pose as risk factors in TBI recovery.

Keywords: sleep, TBI, caffeine, ambien

D8-25

SELECTIVE BRAIN COOLING REDUCES MOTOR DEFICITS INDUCED BY COMBINED TRAUMATIC BRAIN INJURY, HYPOXEMIA AND HEMORRHAGIC SHOCK

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This study examined the effects of selective brain cooling (SBC) on neurobehavioral deficits that were shown to be exacerbated by hypoxemia and hemorrhagic shock (i.e., polytrauma) in a rat model of penetrating ballistic-like brain injury (PBBI). Rats were randomly assigned into two groups (n = 20/group with mortality rate of 33%): PBBI + polytrauma without SBC (control) and PBBI + polytrauma with SBC (SBC). All animals received unilateral 5%PBBI, followed by 30-min hypoxemia (fraction of inspired oxygen = 0.1) and then 30-min hemorrhagic hypotension (mean arterial pressure = 40 mmHg). Fluid resuscitation was given immediately following hypotension. SBC was initiated 15 min after fluid resuscitation and brain temperature was maintained at 32–33°C (core temperature at 37.5°C) for 4 hours under isoflurane anesthesia. Control animals received the same procedures minus the cooling. At 7, 10, 14 and 21 days post-injury, motor function was assessed using the rotarod task. Cognitive function was assessed using the Morris water maze at 13–17 days post-injury. Significant improvement in motor functions were detected in SBC-treated polytrauma animals at 7, 10 and 21 days post-injury compared to the control group ($p < .05$). However, no significant beneficial effects were detected on cognitive measures following SBC treatment in the polytrauma animals. Preliminary data on systemic inflammatory response at 21 days post-injury showed the untreated control group had a slightly higher serum level of interleukin-1 beta (IL-1b) than the SBC group (138 ± 19 vs 121 ± 26 pg/ml), but the difference was not statistically significant. In the presence of polytrauma, TBI patients often require more robust therapeutic interventions to prevent secondary systemic and brain insults. Our data suggested that SBC effectively reduced motor deficits following TBI/polytrauma. Similar findings have been demonstrated in animals subjected to isolated TBI. Such neuroprotective effects may be associated with the reduced inflammatory responses, as reflected by the serum-level of cytokines. Further investigation will focus on cerebral inflammatory response to SBC treatment.

Keywords: Polytrauma, therapeutic hypothermia, selective brain cooling, hypoxemia, hemorrhagic shock

D8-26

EVALUATION OF GLIBENCLAMIDE IN THE WRAIR PBBI MODEL: STUDIES FROM THE OPERATION BRAIN TRAUMA THERAPY (OBTT) CONSORTIUM

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Glibenclamide is a sulfonylurea receptor 1 (SUR1) channel antagonist that is FDA approved for treating Type 2 diabetes. Glibenclamide was selected for testing by the Operation Brain Trauma Therapy (OBTT) Consortium based on published research demonstrating that blocking SUR1 with low-dose glibenclamide provides significant therapeutic benefit in pre-clinical models of stroke and traumatic brain injury (TBI). The current study evaluated the potential therapeutic effect of glibenclamide on neurobehavioral recovery in the WRAIR penetrating ballistic-like brain injury (PBBI) model. Unilateral frontal PBBI was produced in the right hemisphere of anesthetized rats (10% injury severity level). Glibenclamide (Sigma Aldrich) was given as a single dose via intraperitoneal injection (10 μg/kg) at 10 min post-injury, immediately followed by continuous subcutaneous infusion using Alzet osmotic minipumps with infusion rates of 1 μl/h for 7 consecutive days. Motor function and cognitive performance were assessed using the Rotarod and the Morris water maze (MWM), respectively. Brains were perfused and processed for histopathological analysis. Rotarod testing revealed significant motor deficits in all injury groups with overall mean latencies reduced by $42 \pm 9\%$ in the vehicle treated group, and $44 \pm 7\%$ in the glibenclamide treated group ($p < .05$ vs sham). MWM task for cognitive evaluation demonstrated significant deficits in all injury groups with the average latency to locate the hidden platform (average all testing days) increased by $71 \pm 17\%$ in the vehicle treated group, and $92 \pm 19\%$ in the glibenclamide treated group ($p < .05$ vs sham). Additionally, histopathological analysis indicated significant gross morphological changes, including mean lesion volume, in all injured groups. However, no significant therapeutic effects were detected on Rotarod, MWM parameters or on histological metrics. Overall, the results of this study indicate that continuous infusion of low dose glibenclamide was not effective in promoting significant neurofunctional and/or histopathological recovery in the PBBI rat model. Supported by U.S. Army Grant W81XWH-10-1-0623

Keywords: PBBI, Behavior

D9 Poster Session VIII - Group D: Vascular

D9-01

DEVELOPMENT OF ROCK2-SELECTIVE BA-1049 FOR TREATMENT OF CEREBRAL CAVERNOUS MALFORMATIONS

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Cerebral cavernous malformation (CCM) disease is a cerebrovascular disorder in which endothelial cells form single or multiple cystic brain lesions that can leak and cause hemorrhagic stroke and other neurological defects. There is no pharmacological treatment to prevent/reverse CCM lesion formation; severe clinical sequelae are treated by surgical removal of the leaky capillary clusters, potentially causing additional neurotrauma. Inherited cases of CCM are caused by loss of function in one of the 3 CCM genes (*CCM1, CCM2 and CCM3*) and sporadic cases result from mutations in the same genes. Studies of the inherited mutations underlying CCM formation revealed that disruption in endothelial barrier integrity is caused directly by the hyper-activation of Rho, a small GTPase signaling protein that regulates stress fiber formation and cell-cell junctions. We previously demonstrated abnormal activation of Rho after SCI and TBI, and developed BA-1049 as a compound that reverses abnormal activation of downstream Rho kinase (ROCK) in neurotrauma. BA-1049 is selective for the Rock2 isoform highly expressed in cerebral vasculature. To investigate potential efficacy of BA-1049 in CCM, we studied the effect of BA-1049 on endothelial cells. BA-1049 reduces proliferation in human vascular endothelial cells (HUVEC) *in vitro*, suggesting a potential to reverse the angiogenic abnormalities underlying CCM formation. Treatment with BA-1049 also disrupts stress fiber formation and increases occludin/cadherin expression in HUVEC cells, suggesting a potential to reverse the junctional instability and endothelial permeability underlying lesion hemorrhage. To determine if BA-1049 has appropriate properties to be used as an orally active drug, we investigated Caco-2 cell permeability and albumin binding. BA-1049 has good permeability characteristics (Papp Ratio: 1.31) and shows low albumin binding (7.26%). We have performed a computer-based screen of the chemical structure, and no hits indicating potentially serious toxicities were detected. We have focused on CCM for development of BA-1049 because of the clear clinical development path. Success in development of BA-1049 for CCM may lead to further development to reverse Rho activation in other types of neurotrauma, such as TBI.

Keywords: Cerebral Cavernous Malformations, Rho Kinase, Vascular Disorders, CCM, ROCK

D9-02

HUMAN UMBILICAL CORD PERIVASCULAR CELL (HUCPVC) THERAPY FOR TRAUMATIC BRAIN INJURY: TARGETING THE NEUROVASCULAR UNIT

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Mesenchymal stem cells are currently being used in clinical trials for treatment of neurodegenerative diseases including stroke. We were interested in evaluating the potential of human umbilical cord-derived perivascular cells (HUCPVCs), a less differentiated type of MSC, on their therapeutic potential in TBI. HUCPVCs have several advantages over MSCs including ease of procurement and greater rates of expansion.

Objective: We hypothesized that HUCPVCs contribute to recovery of white matter after modeled trauma.

Methods: A gene array analysis was performed on HUCPVCs to examine expression of relevant modulators of inflammation, angiogenesis and neurogenesis. *In vitro* and *in vivo* injury models were used to evaluate HUCPVC treatment on outcome after injury. *In vitro* - E17-derived cortical neurons were cultured for 7 days, then subject to sublethal oxygen-glucose deprivation for 90 minutes resulting in axonal degeneration. HUCPVCs were co-cultured for 3 days and outcome assessed on degenerating axons. *In vivo* - Adult male Sprague-Dawley rats underwent a lateral fluid percussion injury and were treated 24 hours after injury with $2.5x10^6$ fluorescently labeled HUCPVCs via tail vein injection.

Results: Gene expression analysis indicates expression of key neurotrophic (BDNF, NGF, NT3, GDNF), angiogenic (VEGF-A, FGF5, BMP1) and inflammation-modulating factors (CSF, IL members, CXCL members). Preliminary *in vitro* data indicates that HUCPVCs rescue OGD-induced axonal degeneration. *In vivo* results indicate no adverse effects related to HUCPVC treatment. Labeled HUCPVCs were found in the injured cerebral cortex at 24 hrs post-injection.

Conclusions: Our data suggests that HUCPVCs have therapeutic potential to address white matter injury after TBI. Given the immune modulating expression of cytokines, proangiogenic and neurotrophic factor expression there is evidence to suggest that HUCPVCs targets numerous injury mechanisms.

Keywords: stem cell therapy, human umbilical cord perivascular cell, mesenchymal stem cell

D9-03

INSTITUTIONAL REVIEW OF SCREENING FOR BLUNT CEREBROVASCULAR INJURIES

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Introduction: The incidence of blunt cerebrovascular injuries (BCVI) in the trauma population is low; however, the mortality and morbidity associated with symptomatic BCVI approaches 30% and 60% respectively. Appropriate screening methods need to be implemented to ensure treatment is initiated prior to symptom development. Screening algorithms rely mostly on level III evidence. This study evaluates a single institution's data at a Level I trauma center to develop institutional neurosurgical guidelines screening for BCVI.

Methods: IRB for a retrospective review was obtained. The University of Florida Trauma Database was queried. All patients presenting to UF Health since its designation of a Level I Trauma Center (July 1, 2005) with ICD-9 diagnosis codes specific to neurosurgical trauma were individually chart reviewed. Patients included were those who underwent neurovascular imaging and those with a diagnosis of a blunt cerebrovascular injury. Exclusion criteria included patients with a documented history of prior cerebrovascular injury, those with penetrating cerebrovascular injuries, and patients undergoing vascular imaging to assess for intracranial vascular malformation (aneurysm, AVM). Data collected included patient demographics; traumatic injuries; signs, symptoms, treatment, and complications of BCVI; and follow up. A multivariate analysis was performed to determine odds ratios based on trauma findings.

Results: Between July 1, 2005 and July 1, 2014 BCVI incidence was 0.78% of total population (14,505) and 14.7% of those screened (770). There were 113 patients with a BCVI diagnosis (three patients with both); 37 carotid injuries (BCI), 79 vertebral injuries (BVI). Injuries significant for BCVI include C2 fractures, fractures through vertebral transverse foramina, cervical spine fracture dislocations, fractures through the carotid canal, and proximal aortic artery injuries. Stroke rate from injury was 5.3% (13.5% for carotid, 1.2% for vertebral). Treatment practices for BCVI greatly varied with 39% of BVI patients untreated.

Discussion: Incidence of BCVI at a single institution is low. Neurosurgical specific screening model is possible with BVI but difficult with BCI due to low incidence and high stroke rate. Treatment practices varied, however, no treatment of BVI without complications raises question about needing to treat vertebral injuries.

Keywords: BCVI, Blunt Cerebrovascular Injury, Dissection, Stroke

D9-04

A COMPARISON OF THE CEREBRAL VASCULAR EFFECTS OF VANDENBERG OR ADVANCED BLAST SIMULATOR BLAST INJURY IN RATS

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Blast-induced neurotrauma (BINT) is one of the most common causes of mortality and morbidity in military personnel. The development of effective therapies for BINT requires experimental models that replicate important features of BINT in humans. Although neuronal and behavioral effects of BINT have been shown, little is known about its effect on the cerebral vasculature. This study compared the effects of two models of BINT on arterial blood pressure, relative cerebral perfusion, righting reflex and middle cerebral arterial (MCA) diameters during progressive reductions in intravascular pressure.

The Vandenberg model produces blast over/under pressures followed by blunt impact, while the Advanced Blast Simulator (ABS) produces a pure over/under pressure shock wave. We measured relative cerebral perfusion (laser Doppler flowmetry) and arterial blood pressure in adult, male rats that underwent either sham, Vandenberg BINT or ABS BINT. In a separate group of animals, the duration of righting reflex (RR) suppression was recorded following sham, Vandenberg BINT or ABS BINT and the animals were reanesthetized for an additional 60 minutes before being euthanized. The MCAs were then harvested from all animals, mounted on an arteriograph and arterial diameters were measured during progressive reductions in intravascular pressure.

Vandenberg BINT was associated with significant increases in the duration of RR suppression (compared to ABS and Sham). Neither model of BINT produced significant reductions in arterial blood pressure, but both significantly reduced cerebral perfusion and dilator responses to reduced intravascular pressure in isolated MCAs.

These results demonstrate that ABS BINT and Vandenberg BINT significantly impaired dilator responses, specifically cerebral vasodilation in response to reduced intravascular pressure, and suggest that blast exposure, like impact TBI, compromises cerebral pressure autoregulation. These studies were completed as part of an interdisciplinary research team funded by The Moody Project for Translational Traumatic Brain Injury Research.

Support: Moody Project for Translational TBI Research & grant W81XWH-08-2-0132 from the Department of Defense.

Keywords: Vasodilation, Blast Induced Neurotrauma, Advanced Blast Simulator, Cerebral Vasculature, Blast Model

D9-05

THE EFFECTS OF BLAST-INDUCED NEUROTRAUMA ON CEREBRAL VASCULAR, HISTOPATHOLOGICAL AND BEHAVIORAL OUTCOMES

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Introduction: The effects of blast-induced neurotrauma (BINT) on cerebral vascular responses to reduced intravascular pressure in isolated, pressurized middle cerebral arterial (MCA) segments, relative cerebral perfusion and mean arterial pressure (MAP), neuronal injury and cognitive function were measured in rats subjected to BINT using an Advanced Blast Simulator (ABS), a compressed helium-driven shock tube.

Methods: All rats were anesthetized and randomly subjected to BINT or Sham BINT. To measure the effects of BINT on MCA responses to reduced intravascular pressure, rats were anesthetized, prepared for blast and subjected to Sham BINT or BINT (17 – 22 psi)(n = 6/group). Immediately after BINT, righting reflexes (RR) were assessed and MCAs harvested 30 or 60 min later. In a second set of rats, MAP and laser Doppler (LDF) cerebral perfusion were measured before and for two hrs after Sham BINT (n = 10) or BINT (n = 12). A third set of rats were subjected to Sham BINT or BINT (n = 6/group) and euthanized 24 or 48 hrs later for FluoroJade (FJ) staining measurements. A fourth set were subjected to Sham BINT or BINT (n = 10/group) and beam balance and Morris water maze (MWM) performances were tested.

Results: RR suppression in the BINT group was significantly ($P < 0.05$) higher than the Sham group. MAP did not differ significantly between BINT and Sham groups. MCA dilator responses and LDF were significantly reduced ($P < 0.05$) and cerebral vascular resistance significantly increased ($P < 0.0001$) by BINT. BINT resulted in significantly more FJ staining ($P < 0.05$) and significantly impaired beam balance performance ($P < 0.05$). There was a trend ($P = 0.063$) toward increased MWM latencies in the BINT group.

Summary: These results suggest that mild BINT is associated with cerebral arterial constriction and impaired cerebral vascular reactivity that may contribute to impaired behavioral and cognitive function and increased neuronal injury. Furthermore, blast-induced impairment of cerebral dilator responses might contribute to further reductions in cerebral perfusion in the presence of arterial hypotension.

These studies were completed as part of an interdisciplinary research team funded by The Moody Project for Translational Traumatic Brain Injury Research and award W81XWH-08-2-0132 from the Department of Defense.

Keywords: primary blast injury, blast induced neurotrauma, cerebrovascular circulation, cerebral blood flow, behavior

D9-06

TREATMENT WITH DENDRO[60]FULLERENE PRESERVES NEURONS AFTER TRAUMATIC BRAIN INJURY BUT DOES NOT IMPROVE CEREBRAL VASCULAR RESPONSE

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Introduction: TBI results in increased levels of reactive oxygen species (ROS) that can cause cerebral vascular dysfunction. Reduction

of ROS can preserve vascular function and lead to improved outcomes. We tested the antioxidant Dendro[60]fullerene (DF-1) to determine if reducing ROS levels would improve outcomes after TBI.

Methods: For all experiments, male Sprague-Dawley rats received either sham, moderate fluid percussion TBI alone or TBI followed by treatment with DF-1 (10 mg/kg, i.v.) one hour post-injury. For experiments to determine DF-1's effects on the vasodilatory responses, middle cerebral arteries (MCA) were harvested two hours after injury. The MCA's response to reduced intravascular pressure was assessed by measuring MCA diameters after incremental decreases in pressure from 100 to 20 mmHg. For FluoroJade C (FJC) experiments, animals were euthanized 24 hours after injury. Brains were harvested, stained and the numbers of FJC positive neurons in the hippocampus were counted. In a third group of animals, beam balance and beam walk testing was done on days 0 to 4 and Morris water maze (MWM) testing was completed on days 11 to 15 after injury.

Results: MCA vasodilatory responses were not significantly improved by DF-1. In contrast, the total number of FJC positive cells were significantly decreased with DF-1 treatment. DF- 1 treatment also significantly ($p < 0.05$ vs TBI alone) improved performance in the MWM and beam walk tasks. DF-1 treatment did not significantly improve beam balance performance.

Discussion: Our results that DF-1 does not improve the cerebral vasodilatory response are consistent with our previous physiological studies of MAP, CVR and cerebral perfusion. However, DF-1 did reduce neuronal cell death in the hippocampus and improve outcome in behavioral testing. Since carboxyl-functionalized fullerenes such as DF-1 cross the blood brain barrier, their neuroprotective properties may be related to antioxidant actions within the brain parenchyma.

Keywords: Nanotechnology

D9-07

PERIPHERAL BLOOD MARKERS OF VASCULAR INJURY IN MODERATE-TO-SEVERE TBI - RELATIONSHIP TO SYSTEMIC CATECHOLAMINES AND OUTCOME

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Background: Traumatic brain injury (TBI) causes damage to the neurovascular unit, resulting in the release of associated molecules that cross the disrupted blood-brain barrier into the systemic circulation. Additionally, sympathetic activation accompanying TBI may exacerbate endothelial damage. However, few clinical studies have assessed vascular injury molecules in relation to catecholamines and neurological outcome after TBI.

Purpose: To evaluate a panel of soluble endothelial activation/injury molecules in moderate-to-severe TBI patients; determine possible associations of these markers with circulating catecholamine levels and 6-month neurological outcome assessed by extended Glasgow Outcome Scale (GOSE).

Methods: Peripheral blood was drawn from 181 TBI patients ($N = 138$ severe, $N = 43$ moderate) on admission, 6-, 12-, and 24-h post-injury; control samples were collected from healthy volunteers ($N = 21$). Plasma concentrations of endothelial-selectin (E-selectin), platelet selectin (P-selectin), c-reactive protein (CRP), serum amyloid-A (SAA), thrombomodulin (TM), intercellular adhesion molecule (ICAM) −1, −3, and vascular cell adhesion molecule (VCAM)-1, were quantified using a ultra-sensitive MULTI-ARRAY immunoassay. Plasma epinephrine (Epi) and norepinephrine (NE) levels were evaluated by ELISA.

Results: Within 24 h of admission, TBI patients showed significant differences in concentrations of all vascular injury molecules compared to controls, with the exception of TM. At admission only P-selectin differed from controls. Differences between moderate and severe TBI were observed in E-selectin and ICAM-3. High admission catecholamine values were associated with alterations in TM, P-selectin, ICAM-1, CRP and SAA. Elevated levels of TM and P-selectin were associated with unfavorable 6-month outcome and mortality; mortality was also associated with elevated admission levels of ICAM-1.

Conclusion: Moderate-to-severe TBI is characterized by alterations of plasma vascular injury/activation biomarkers. These markers are associated with poor outcome at 6-months and may be mediated by enhanced sympathetic activation.

Keywords: TBI, Vascular Injury, outcome, catecholamines

D9-08

FUNCTIONAL NEAR INFRARED SPECTROSCOPY (FNIRS)- 2 NON-INVASIVE METHODS TO ASSESS TRAUMATIC VASCULAR INJURY AFTER TBI

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Objective: Assess 2 methods, fNIRS with hypercapnia (NIRS-CO_2) and cognitive (NIRS-COG) challenges, of cerebrovascular reactivity (CVR) among healthy control (HC) and traumatic brain injury (TBI) subjects.

Background: Injury to cerebral blood microvessels is a well-recognized consequence of TBI. Functional Near-InfraRed Spectroscopy (fNIRS) can non-invasively measure changes in oxyHb concentration. It is less expensive and easier to use in outpatient settings than MRI-based technologies.

Design/Methods: We devised two fNIRS testing paradigms- NIRS partnered with frontal lobe activation and hypercapnia challenges. We tested 22 TBI subjects, and 15 age/gender-matched HC with NIRS-CO_2 and MRI-BOLD with hypercapnia challenge. We also tested 32 TBI and 15 HC with NIRS-COG and abbreviated neuropsychological testing. In both NIRS-CO_2 and MRI-BOLD, hypercapnia was induced with a Douglas bag fitted with a valve that supplied room air alternating each minute with room air mixed with 5% carbon dioxide (CO_2). CVR was calculated as a percentage of change in the blood concentration (NIRS-CO_2) or MRI-BOLD signal divided by the variation of $EtCO_2$(CVR = ΔHb /$\Delta EtCO_2$or%ΔBOLD signal/$\Delta EtCO_2$). With NIRS-COG, we measured the changes in regional blood concentration between two different cognitive loads.

Results: TBI subjects have lower and more variable CVR values than HC (NIRS-CO_2: TBI mean 0.293 ± 0.039; HC, mean 0.336 ± 0.014; $p = 0.0085$) and correlates with neuropsychological testing. Global CVR measured with BOLD fMRI is highly correlated with CVR in frontal regions measured by NIRS-CO_2 ($R^2 = 0.68$). For NIRS-COG measurement, TBI have a higher blood volume ratio than HC (NIRS-COG: TBI mean 1.35; HC mean 1.18, $p = 0.027$).

Conclusions: fNIRS combined with hypercapnia challenge or cognitive testing are practical, noninvasive methods to assess vascular function after TBI and are both less expensive and more portable than MRI-based technologies. These results support the use of both fNIRS methods as biomarkers for clinical trials of vascular-directed therapies.

Keywords: Near InfraRed Spectroscopy, cerebrovascular reactivity, hypercapnia challenge, functional NIRS testing

D9-09

HEME OXYGENASE-1 AND LIPOCALIN-2 INTERACTION DURING HEME PROCESSING AFTER TRAUMATIC BRAIN INJURY

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Heme Oxygenase-1 (HO-1), the inducible form of Heme Oxygenase, degrades heme into biliverdin, CO, and iron. It is a heat shock protein, robustly induced by CNS vascular hemorrhage following traumatic brain injury (TBI). Notably, HO-1 activity releases highly oxidative iron, which can promote local pathology, as well as up-regulate transcription to buffer acute free radical damage, and potentially affect neural plasticity during postinjury recovery. HO-1 production is partially self-regulated via induction of Nrf2 signaling; Nrf2 is a transcription factor that activates the consensus antioxidant response element targeting numerous antioxidant genes. We hypothesized that time dependent HO-1/NRf2 axis activation post-TBI mediates iron processing pathways to influence tissue recovery. Using rat central fluid percussion TBI, post-injury HO-1 protein expression in hippocampus (HC) and cortex (CTX) was compared with downstream biliverdin/bilirubin deposition and level of iron transport protein lipocalin-2 (LCN2). Western blot (WB) analysis demonstrated that HO-1 protein peaks 3d post-injury and persists until 7d in HC and CTX. CTX HO-1 is differentially distributed over post-injury time, initially found in GFAP+ astrocytes, then increasingly expressed by IBA1+ cells localized at necrotic sites and around small vessels. A 3d peak in HO-1 expression is consistent with the documented time course of heme release/degradation after brain injury. Interestingly, HC also exhibits a similar HO-1 protein expression profile without overt hemorrhage. Optical analysis shows sequential evolution of biliverdin and bilirubin deposition in the CTX through 7d. Paired Perls stain revealed cellular iron deposition by 3d, indicating onset of significant heme degradation. Further, WB analysis shows high LCN2 expression immediately post-injury, peaking at 1d and declining at 3d and 7d. Preliminary microarray gene profiling supports HO-1 transcript elevation at 1d and 7d; also transient acute mRNA increase in LCN2 at 1d post-injury. Overall, our results reveal time dependent HO-1 activation and potential interaction with LCN2 to mediate heme/iron processing following TBI. The data also suggests that delay in post-injury heme accumulation/breakdown, along with ongoing elevation of heme lytic products and iron transporters, may expand the therapeutic window for post-injury buffering of hemorrhage-induced pathology. Support: NIH-NS056247/NS057758.

Keywords: Heme Oxygenase 1, Lipocalin 2, Iron Metabolism, Heme Metabolism

D9-10

AXONAL INJURY AND NEUROBEHAVIORAL IMPAIRMENT AFTER SUBARACHNOID HEMORRHAGE

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The great majority of acute brain injury results from trauma or from disorders of the cerebrovasculature. Although traumatic and vascular brain injuries are generally considered separately, brain hemorrhage shares many physiological parallels with trauma, and both result in debilitating chronic neurocognitive deficits. Aneurysmal subarachnoid hemorrhage (SAH) is the most devastating variant of hemorrhagic brain injury, carrying a 1-month mortality rate of nearly 50%. The underlying causes of neurocognitive deficits in SAH are unknown and invisible to clinical imaging modalities. We recently found that SAH induces radiological and pathological axonal injury similar to that seen after trauma. We therefore sought to develop a mouse model of SAH-induced neurobehavioral deficits to determine whether axonal injury is a key correlate of long-term neurobehavioral sequelae in SAH, as it is following trauma. We developed a SAH induction and post-SAH screening protocol that yields multi-domain neurobehavioral deficits in memory and cognition (Morris Water Maze test), depression- and anxiety-related behaviors (tail suspension and elevated plus maze tests), and in social behavior (social interaction test). These impairments parallel those reported by patients after brain hemorrhage and trauma. We furthermore developed an advanced diffusion MRI approach involving diffusion kurtosis and generalized q-sampling imaging with paired histological analysis to define radiological biomarkers of acute brain injury pathways following SAH, and to correlate these biomarkers with neurobehavioral outcomes. Our results demonstrate that post-hemorrhagic neurobehavioral outcomes can be analyzed in a highly tractable model organism, and lay the groundwork for mechanistic analysis of these outcomes using clinically translatable radiological biomarkers. These findings and approaches are likely to have application to post-traumatic neurocognitive deficits as well.

Keywords: subarachnoid hemorrhage, MRI, diffusion tensor imaging, behavior

Speaker Presentation Abstracts

AANS01 Acute Challenges in the Unstable Spine

AANS01-01

CERVICAL TRACTION FOR THE TREATMENT OF UNSTABLE SUBAXIAL INJURIES

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Following acute cervical spine trauma, traction can be used to restore sagittal plane alignment in patients with subaxial injuries. Furthermore, it can reduce unilateral or bilateral cervical facet dislocations, and to improve alignment in patients with traumatic spondylolisthesis of the axis. We here report our institutional experience treating both adult and pediatric patients with acute unstable cervical spinal trauma using skull traction +/− surgical stabilization. Our experience suggests that the use of cervical traction may obviate the need for operative treatment for some patients with atlanto-axial rotatory subluxation. Additionally, our use of perioperative and intraoperative spinal traction has been shown to assist with preoperative planning and to improve overall correction and pulmonary function in patients with spinal deformity. Our data suggest that the most common complications associated with cervical spine traction include pin-site infection, pain and neuroma formation; however, more serious neurological complications, including cranial nerve palsy and spinal cord injury, although rare, could also occur; thus, careful monitoring of patients undergoing traction is essential. A review of the literature is provided.

Keywords: unstable spine, cervical traction, spinal injury

AANS01-02

LATERAL APPROACH TO SPINE TRAUMA

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Traditionally, several approaches have been utilized to address spinal trauma pathologies. Such posterior approaches include the laminectomy, transpedicular and costotransversectomy approaches. Traditional anterior approaches include open thoracotomy and endoscopic thoracotomy. These traditional approaches allow for varying degrees of neural decompression, but they are also generally highly morbid. The lateral approach for spine trauma allows for a significant neural decompression and placement of a robust vertebral body replacement device with minimized morbidity. This approach was studied by Drs. Dakwar, Le, Uribe, and Smith (*Minimally Invasive Surgery for Traumatic Spinal Pathologies.* Spine. Volume 35, Number 26S, ppS338-S346). In a series of 52 patients, key findings include average operative time of 128 mins, average estimated blood loss of 300 mL, avoidance of chest tube placement in all but 2 cases, and a 13.5% complication rate. The presenter has also studied the impact of utilizing the lateral approach within 4 hours of injury to treat patients with complete motor and sensory deficit at the level of fracture. In a series of 8 patients treated within this criteria, 4 patients improved ASIA by 2 or more levels, and no significant surgical related morbidities occurred. In conclusion, the lateral approach provides significant clinical benefits over traditional approaches for the treatment of spinal trauma.

Keywords: Minimally Invasive Surgery, Lateral approach/fixation, XLIF, Corpectomy, Neural decompression, Vertebral fracture

AANS01-03

TRAUMATIC THORACOLUMBAR SPINAL INJURY: AN ALGORITHM FOR MINIMALLY INVASIVE SURGICAL MANAGEMENT

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Object: Minimally invasive spinal (MIS) surgery techniques have been used sporadically in thoracolumbar junction trauma cases in the past 5 years. A review of the literature on the treatment of thoracolumbar trauma treated with MIS surgery revealed no unifying algorithm to assist with treatment planning. Therefore, the authors formulated a treatment algorithm.

Methods: The authors reviewed the current literature on MIS treatment of thoracolumbar trauma. Based on the literature review, they then created an algorithm for the treatment of thoracolumbar trauma utilizing MIS techniques. This MIS trauma treatment algorithm incorporates concepts form the Thoracolumbar Injury Classification System (TLICS).

Results: The authors provide representative cases of patients with thoracolumbar trauma who underwent MIS surgery utilizing the MIS trauma treatment algorithm. The cases involve the use of mini-open lateral approaches and/or minimally invasive posterior decompression with or without fusion.

Conclusions: Cases involving thoracolumbar trauma can safely be treated with MIS surgery in select cases of burst fractures. The role of percutaneous nonfusion techniques remains very limited (primarily to treat thoracolumbar trauma in patients with a propensity for autofusion [for example, those with ankylosing spondylitis).

Keywords: Minimally invasive spinal (MIS) surgery, Thoracolumbar Injury Classification System (TLICS), burst fractures, thoracolumbar trauma

AANS02 Acute Surgical Cranial Trauma - To Drill or Not To Drill: That Is the Question

AANS02-01

CONTROVERSIES IN INTRACRANIAL MONITORING

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ICP monitoring is standard of care in most developed countries for patient with severe TBI. Over the last decade or more other modalities have been monitored in these patients: cerebral blood flow, partial brain oxygenation pressure, seizures, spreading depression, and brain metabolites, just to name a few. The efficacy of such will be discussed in this presentation.

Keywords: Multimodality monitoring, Brain oxygenation, Intracranial pressure, EEG

AANS02-02

PRECISION MEDICINE FOR ICP TREATMENT: TCD INDIVIDUALIZES TARGETING COMPLIANCE AND/OR PERFUSION AMELIORATION

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Transcranial Doppler (TCD)-derived parameters can classify patients into four categories: a group of patients at risk of raised intracranial pressure (ICP) could benefit from ICP reduction by osmotherapy alone, another group could benefit from blood pressure augmentation alone, a third group would benefit from dual-targeted treatment, while a fourth group with normal physiology could receive no treatment.

TCD was performed for non-invasive ICP monitoring in 5 patients in our ICU with cerebral edema and risk for ICP-related ischemia, but who were non-surgical or at high bleeding risk for ventriculostomy. Cases were 1 hepatic failure and 1 meningitis, both with global cerebral edema (GCE) and hemispheric hematoma with midline shift (MLS), 1 moderate traumatic brain injury (TBI) and 2 hypertensive hematomas with mass effect. TCD was used to derive pulsatility index (PI) as a surrogate marker for brain compliance and end-diastolic velocity (EDV) reflecting adequacy of cerebral perfusion pressure (CPP). We applied therapeutic choices according to the 4 described categories to specifically address the cerebral needs of each group.

One patient had no change in management because of normal PI and EDV. Two received hypertonic saline along with induced hypertension. One patient received mannitol and had vasopressors tapered off to address break-through pressure edema. One patient received hemodynamic augmentation for CPP amelioration. All patients had normalization of PI and EDV within our target range within an hour of the tailored therapy. No patient had neurological deterioration, worsening of GCE, MLS, new hemorrhage or developed infarcts within 48h of our repeated interventions.

TCD was helpful to tailor a better suited therapeutic intervention within this novel treatment paradigm. We propose to refine goal-directed therapies for the pleiomorphic entity of cerebral blood flow compromise instead of focusing solely on elevated ICP.

Keywords: Transcranial doppler, Brain Compliance, Cerebral perfusion, Goal-directed therapy

AANS02-03

MANAGEMENT OF ACUTE NEUROVASCULAR INJURY

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Background: Arterial and venous structures are frequently involved in neurotrauma. Risks of surgical complications and overall morbidity and mortality are high. Objectives: Demonstrate neurovascular injuries and principles of management.

Methods: Case studies are used to illustrate critical injuries, technical nuances of the interventions and outcomes.

Results: Penetrating injury at the superior sagittal sinus was managed conservatively. Traumatic carotid-cavernous sinus fistula was successfully closed endovascularly. Laceration of the torcular was managed with angiography in the hybrid endovascular surgical suite and open surgical repair. Lacerations of meningeal and cortical vessels were repaired surgically in open depressed skull fracture. Transection of the vertebral artery was managed with endovascular vessel sacrifice. Good functional outcomes were achieved in all cases with no surgical morbidity or mortality.

Conclusions: Recognition of neurovascular anatomy at the site of injury is crucial for the choice of treatment strategy. Good outcomes and low surgical morbidity can be achieved.

Keywords: neurovascular, carotid cavernous fistula, vertebral artery transection, torcular laceration, interventional treatment, surgical management

AANS03 Outcomes after Spine Trauma

AANS03-01

DOES TIMING MATTER?

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Neurologic function, spinal column stability, or both may be affected by spine trauma. Historically, the timing of surgical treatment of these conditions has been controversial. In this session, the history of and the more recent evidence supporting early surgery following spine trauma will be reviewed. Specifically, the Surgical Trial in Acute Spinal Cord Injury Study (STASCIS) data will be presented. Early decompression (within 24 hours) should be considered as part of the therapeutic management of any patient with spinal cord injury (SCI). Very early decompression (within 12 hours) should be considered for any patient with an incomplete cervical SCI.

Keywords: spinal column stability, acute SCI

AANS03-02

LUMBOSACRAL SPINAL CORD EPIDURAL STIMULATION FOR STANDING AFTER CHRONIC COMPLETE PARALYSIS IN HUMANS

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Motor complete spinal cord injury has been considered functionally complete resulting in permanent paralysis with no recovery of voluntary movement, standing or walking. In this study, we showed that two clinically sensory and motor complete participants were able to stand over-ground bearing full body-weight without any external assistance, using their hands to assist balance. The other two clinically motor complete participants also used minimal external assistance for hip extension. The combination of stand training and improvement of

stimulation parameters promoted standing with the least amount of assistance, which was achieved with overall continuous EMG patterns of the lower limbs' muscles. Stimulation parameters optimized for one individual resulted in poor standing and additional need of external assistance for hip and knee extension in the other participants. During sitting, little or negligible EMG activity of lower limb muscles was induced by epidural stimulation showing that weight-bearing related sensory information was needed to generate sufficient EMG patterns to effectively support full weight-bearing standing. In general, electrode configurations with cathodes selected in the caudal region of the array at relatively higher frequencies (25–60 Hz) and near-motor threshold amplitudes resulted in the more effective EMG patterns for standing. These results show that human spinal circuitry can generate motor patterns effective for standing in the absence of functional supraspinal connections; however the appropriate selection of stimulation parameters is critical.

Keywords: epidural stimulation, standing, spinal cord injury, recovery of motor function

AANS03-03

ARE STEM CELLS THE ANSWER?

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Stem cells have been recog-nized and in-tensively studied for their potential use in restorative appro-aches for traumatic injuries to the spinal cord. In stem cell-based strategies, the cells have been pro-posed to replace neu-ronal, astro-cyte, oligo-dendro-cytes loss and also con-tribute to neo-vascularization. This review will dis-cuss some of the preclinical studies supporting the use of stem cells after SCI. The focus will be on the use of bone marrow stromal cells (BMSCs) / mesenchymal stem cell as well as neural stem cells for the repair of the spinal cord injury (SCI). A review of the ex-tent of stem cell tourism for SCI will be demon-strated. Also some of the pre-liminary data on the use of neural stem cells for chronic SCI will be dis-cussed.

Keywords: cell-based strategies, BMSCs, spinal cord, SCI

AANS04 Outcomes after Cranial Trauma

AANS04-01

LONG TERM FUNCTIONAL OUTCOMES AFTER HEMICRANIECTOMY FOR TRAUMA

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Hemicraniectomy has gained recent popularity in management of both pediatric and adult head injury in patients with incipient or established brain swelling. The exact indications, techniques, and outcomes remain controversial. While a number of studies have shown improvements in mortality, morbidity and complications remain significant. This talk will compare some of the available studies in this area, with particular emphasis on key differences in populations studied and methodologies which may underlie differences in conclusions about the utility and long-term outcomes after hemicraniectomy procedures. Suggested approaches for decision-making about when and in whom to utilize this technique will be outlined, as well as research gaps which still need to be filled for more definitive guidance.

Keywords: Surgery, Decompression, Craniotomy, Outcome

AANS04-02

HOW STRONG IS THE EVIDENCE LINKING TRAUMA AND/OR TAU TO DEMENTIA

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One of the most feared long term consequences of traumatic brain injury (TBI) is the development of dementia. Multiple epidemiologic studies have shown that experiencing a TBI in early or midlife is associated with an increased risk of dementia in late life. The best available data indicate that an episode of moderate to severe TBI increases the subsequent risk for the development of dementia between 2- and 4-fold. It is less clear whether mild TBI results in increased dementia risk, in part because mild head injuries are often not well documented and retrospective studies have inherent recall bias. However, it is well understood that multiple mild TBIs, as experienced by professional boxers and football players are associated with a high risk of chronic traumatic encephalopathy (CTE), a type of dementia with distinctive clinical and pathologic features. The recent recognition of many cases of CTE among retired professional football and hockey players has stimulated great interest in this unique condition characterized by the widespread accumulation of the microtubule-associated protein *tau*, in neurons and astrocytes. In association with the prolonged and repeated deployments to Iraq and Afghanistan, there has been the recognition that military personnel also experience high rates of mild TBIs and may develop a similar syndrome. A recent study has shown an increased risk of dementia among older Veterans who had previously experienced TBI (Barnes, DE, et al. *Neurology* 83: 312–319, 2014). Because virtually all epidemiologic studies linking prior episodes of TBI with late life dementia have lacked postmortem examination, it remains unclear if this association relates to the subsequent development of Alzheimer's disease, CTE or some other entity. There is clearly need for detailed neuropathologic evaluations of incident cases of dementia following prior episodes of TBI and the inclusion of postmortem examination in epidemiologic studies relating dementia with prior TBI.

Keywords: dementia, tau, neuropathology, CTE, Alzheimer's disease

AANS04-03

PREVALENCE OF VISION PROBLEMS AFTER CONCUSSION IN CHILDREN 11–17 YEARS OLD

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Vision problems, including binocular vision disorders, accommodative disorders, such as convergence insufficiency, and eye movement/saccadic disorders have been found after concussion in the adult population, both military and civilian. Symptoms are associated with prolonged visual near work, including eye strain, headaches, blurred/double vision. There are currently no prospective studies on the prevalence of vision problems in adolescents following concussion.

Participants were recruited from the Minds Matter Concussion Program at The Children's Hospital of Philadelphia for this prospective, cross-sectional study. Patients with the diagnosis of concussion underwent vision testing, including an assessment of visual

symptoms, visual acuity, eye alignment, near point of convergence, vergence amplitude/facility, accommodative amplitude/facility, and saccadic eye movement speed and accuracy.

72 children were examined with a mean age of 14.6 years. 49/72 (68%) had one or more vision problems. The most common problems were convergence insufficiency (47.2%), accommodative insufficiency (33.3%), saccadic dysfunction (30.5%), and accommodative infacility (11.1%). 64% with convergence insufficiency also had an accommodative disorder. The Convergence Insufficiency Symptom Survey (CISS) was used to assess visual symptoms. The mean CISS score for children without a vision problem was 13.2 vs. 21.4 in children diagnosed with significant vision problems ($p = 0.001$). There was no significant difference in the prevalence of vision problems when comparing recent (<3 months) vs. longstanding (>3 months) concussion injury. Patients with a vision problem also had deficits in verbal memory and visual motor scores on computerized neurocognitive testing ($p = 0.016$ and $p = 0.0074$).

A high prevalence of oculomotor disorders (binocular vision, accommodative, and eye movement) was found in this sample of adolescents with concussion. These results suggest that a vision examination that specifically evaluates oculomotor function should be a part of the evaluation of concussion.

Children may be particularly vulnerable to the consequences of such deficits after concussion due to their full-time academic work at school.

Keywords: vision, vestibular, oculomotor, concussion

PL01 New Investigators and New Visions for CNS Iinjury Research

PL01-01

ENHANCING RESPIRATORY PLASTICITY FOLLOWING CERVICAL SPINAL CORD INJURY

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Impaired breathing is a devastating consequence of cervical spinal cord injury (SCI), representing a significant burden to injured people and increasing the risk of mortality. This is due in part to the direct compromise of the phrenic motor system that controls diaphragm function. While there is mounting evidence for spontaneous improvements in phrenic function and respiration, the extent of recovery – or functional plasticity – remains limited. The neuroplastic changes contributing to this recovery remain a subject of ongoing research. However, recent experimental studies suggest that spinal interneurons contribute to phrenic plasticity and represent a therapeutic target for enhancing functional recovery post-SCI. Capitalizing on the potential of these cells, the goal of the present work is to test whether transplantation of interneuron-rich neural precursor tissue can restore anatomical continuity, contribute to formation of novel interneuronal relays, and enhance diaphragm recovery.

Adult, female Sprague Dawley rats received lateralized C3/4 contusion injuries and were allowed to recover for 1 week. At that time, the injury site is re-exposed and allogeneic donor tissue (from developing rat spinal cord) was transplanted directly into the lesion epicenter. Ventilation was assessed using whole-body plethysmography weekly pre- and post-injury. One month post-injury, transneuronal tracing was then used to examine the extent of synaptic integration between i) host and donor neurons, and ii) transplanted cells and host phrenic circuitry. One month post-transplantation, terminal neurophysiological studies were used to assess phrenic function, and record activity from transplanted neurons.

These experiments revealed that transplanted cells survive, proliferate, restore tissue continuity and become synaptically integrated with host phrenic circuitry. Host neurons also become integrated with donor cells. Terminal electrophysiology has shown improvement in phrenic function in transplant recipients. Multiunit recordings made from within transplanted tissue have revealed phasic patterns of activity consistent with inspiration. These results suggest that transplantation of neural progenitor tissue from the developing spinal cord may contribute to an interneuronal relay capable of improving diaphragm recovery following cervical SCI.

Keywords: spinal cord injury, phrenic, interneuron, neural precursor, respiration

PL01-02

RNA SPLICING IN CNS DAMAGE: DIAGNOSING THE INJURED SPLICEOSOME

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Most mammalian genes encode one or more mRNA transcripts which give rise to multiple protein variants having altered or opposing biological function. Acute brain injury or progressive neurodegenerative disease disrupts spliceosomes – sites of active RNA splicing in the nucleus. Different protein splicing factors (SFs), which modulate variant selection of distinct gene sets, are also disturbed by injury. Aberrant SF balance could favor translation of detrimental protein variants. Characterizing the functions of enigmatic SFs in brain, including identification of their unique mRNA targets, may yield new insights into molecular sequelae causing neuronal dysfunction after injury. SFs may also represent novel therapeutic targets – inhibiting or activating key SFs could be used to correct splicing perturbations caused by damage. Here we focus discussion of this topic on the splicing factor RNA Binding Motif 5 (RBM5), and in the setting of experimental TBI. In brain, nuclear RBM5 mostly localizes to neurons, and this finding is supported by *in vitro* evidence. After combined control cortical impact (CCI) + hemorrhagic shock (HS) in mice, RBM5 appears upregulated throughout the ipsilateral hippocampus and cortex. Findings here expand understandings of splicing dysregulation after TBI and offer new concepts for future therapies.

Keywords: RNA Splicing, RNA Binding Motif 5, Controlled Cortical Impact, Hemorrhagic Shock

PL01-03

PLASTICITY IN THE CORTICOSPINAL SYSTEM AFTER SPINAL CORD INJURY

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The corticospinal tract is an important target for motor recovery after spinal cord injury (SCI) in animals and humans. Using non-invasive electrophysiological techniques we have demonstrated the presence of plasticity in corticospinal projections targeting spinal motoneurons of muscles located close and at a long distance from the injury site in humans with chronic anatomically incomplete cervical SCI. We developed tailored protocols for precisely timing the arrival of descending and peripheral volleys at corticospinal-motoneuronal synapses of hand muscle in humans with chronic incomplete SCI. We found that the arrival of presynaptic volleys prior to motoneuron discharge enhanced corticospinal transmission and hand voluntary motor output. These findings are the first demon-

stration that spike timing-dependent plasticity of residual corticospinal-motoneuronal synapses provides a mechanism to improve motor function after SCI. Modulation of residual corticospinal connections may present therapeutic target for enhancing voluntary motor output in motor disorders affecting the corticospinal tract.

Keywords: Motor control, Voluntary Movement, Transcranial Magnetic Stimulation, Plasticity

PL02 Therapeutic Hypothermia and Targeted Temperature Management after SCI and TBI - Is the Verdict Still Out?

PL02-01

PERSPECTIVES ON HYPOTHERMIA AFTER TBI AND SCI - REVIEW OF NEW BASIC RESEARCH IN TEMPERATURE MANAGEMENT

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Over the past several decades, basic, translational and clinical research has evaluated the beneficial effects of therapeutic hypothermia (TH) in a number of neurological conditions. These temperature studies have provided a useful experimental tool by which to clarify temperature sensitive injury mechanisms related to long term functional outcomes. Today we know that relatively mild reductions, or increases in brain or spinal cord temperature during or following neurotrauma or cerebral ischemia can significantly alter multiple injury pathways associated with neuronal dysfunction and death as well as functional deficits. Recently new exciting data has emerged implicating novel cell signaling pathways, innate immunity and genetic targets including several temperature sensitive microRNAs related to this topic. The fact that these same injury pathways are current drug targets for the development of new therapeutic strategies emphasizes the importance of targeted temperature management (TTM) strategies in the acute and subacute injury settings. More recently the importance of posttraumatic brain temperature on reparative strategies has also been discussed where studies have reported the beneficial effects of TH in enhancing reparative processes including neurogenesis. The ability of relatively minor temperature modifications including mild hyperthermia to alter the brain's vulnerability to an insult such as concussion while also playing a critical role in influencing secondary injury and reparative processes emphasizes the need to take advantage of TTM practices to successfully protect and treat our neurotrauma patients. Clinical investigations are investigating new systemic cooling strategies using both surface and endovascular approaches while local cooling approaches are also being considered. The recent provocative findings emphasizing the possible increased importance of TTM and fever control versus TH again points to a need to continue basic and translational research in neurotrauma. It's clear that this is a fertile area for continued medical research that should provide important new information that can hopefully be translated to our patient populations to improve long term outcomes.

Keywords: hypothermia, hyperthermia, targeted temperature management

PL02-02

HYPOTHERMIA FOR TRAUMATIC BRAIN INJURY: IT WORKS WITH CORRECT PATIENT SELECTION

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Hypothermia in the treatment of traumatic brain injury is under intense investigation for a very specific subtype of TBI patient. Subdural hematomas (SDH) occur in $\sim$45% of severe TBIs, with a mortality above 60%, causing approximately 1 million deaths annually worldwide. The high mortality associated with acute SDHs can be lowered by rapid surgical intervention and aggressive medical management; nonetheless, acute SDH remains one of the most common causes of death due to TBI. Hypothermia has been shown to improve histopathological and behavioral consequences of TBI using various experimental models. However, twenty-three hypothermia clinical trials involving 1614 patients with TBI have yielded inconsistent results. Two randomized, multi-center trials of hypothermia induction in patients with severe TBI performed in the United States (NABIS:HI and NABIS:HII) were stopped due to futility, with no improvement in neurologic outcomes. The lack of statistical effect was attributed in part to the heterogeneity of brain injuries. Indeed, a retrospective subgroup analysis of these trials revealed that hypothermia improved neurologic outcomes in the subset of TBI patients undergoing surgical evacuation of acute SDHs. These results have led us to the design and initiation of the HOPES trial (HypOthermia for Patients requiring Evacuation of Subdural Hematoma), a prospective, randomized clinical trial to study the effects of *very early hypothermia* in patients undergoing surgical evacuation of acute SDH. This trial will also assess whether the beneficial effects of hypothermia are related to blunting ischemia/reperfusion injury and/or blunting the incidence of cortical spreading depolarizations. The current role and future direction of hypothermia and temperature management in TBI will be reviewed and discussed.

Keywords: hypothermia, cortical spreading depression, reperfusion injury, clinical trial, craniotomy,

PL02-03

THERAPEUTIC HYPOTHERMIA AND TARGETED TEMPERATURE MANAGEMENT AFTER SCI AND TBI - IS THE VERDICT STILL OUT?

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Systemic hypo-thermia remains a pro-mising neuro-pro-tective strategy for both spinal cord (SCI) and head injury (HI). We describe our ex-tended single center experience using in-tra-vascular hypo-thermia for the treat-ment of cervical SCI. Forty-five acute cervical SCI patients have now received modest (33 C) in-tra-vascular hypo-thermia for 48 h. Neuro-logical outcome was assessed by the Inter-national Standards for Neuro-logical Classification of Spinal Cord Injury scale (ISNCSCI) de-velop-ed by the American Spinal Injury Association. Local and systemic complications were recorded. All patients were complete ISNCSCI A on admission, but four con-verted to ISNCSCI B in 24 h post injury. The ISNCSCI con-version rate of at least one grade was appro-ximately 43% at latest fol-low up 10.07 ($\pm$1.03) months. The overall risk of any thromboembolic complication was 14.2%. The results are promising in terms of safety and impro-vement in neuro-logical outcome. To date, the study repre-sents the largest study cohort of cervical SCI patients treated by modest hypo-thermia. A multicenter, randomized study is needed to determine if systemic hypothermia should be a part of SCI patients' treat-ment for whom few options exist. A review of the status of hypo-thermia for closed HI will also be dis-cussed.

Keywords: head injury, ISNCSCI, spinal cord

PL03 Executive Function after Experimental and Clinical TBI

PL03-01

A COMBINED THERAPY OF ENVIRONMENTAL ENRICHMENT AND CITALOPRAM AMELIORATES ATTENTIONAL SET-SHIFTING PERFORMANCE AFTER BRAIN TRAUMA

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Traumatic brain injury (TBI) models in the laboratory have been associated for decades with declines in long-term learning and memory, although the types of behavioral tests performed to date did not focus on the complex attention impairments related to the frontal lobe, which are common in most brain injuries. Specifically, executive function and cognitive flexibility represent sophisticated brain capabilities to use environmental feedback to ''unlearn'' a previously valid set of rules, switch gears and filter out unwanted distractions. We have begun to employ the attentional set-shifting test (AST), a complex cognitive paradigm analogous to the Wisconsin Card Sorting Test, which is used to measure strategy-switching deficits in patients with frontal lobe damage, TBI, and psychiatric disorders. Previously, we demonstrated that a controlled cortical impact (CCI) injury produced significant impairments in executive function and cognitive flexibility in the AST. In the current study, clinically relevant therapies for cognitive performance deficits after traumatic brain injury were used alone and in combination. Specifically, the enriched environment (EE) housing strategy is an endorsed animal model of rehabilitation, while daily injections of the antidepressant drug citalopram, a treatment known to alleviate depressive-like symptoms and improve cognition in humans, were also provided alone or in combination with EE. The combined treatment aims to mimic simultaneous rehabilitation and pharmacological treatments given to patients in a clinical setting. Four weeks post-surgery, EE exposure provided significant cognitive recovery after injury, although performance may further benefit from combined therapy with citalopram, as preliminary findings indicate. Future studies will continue to investigate in more detail the ideal cognitive recovery timeline and specific brain pathways and mechanisms involved in restoring higher function after TBI.

Keywords: executive function, environmental enrichment, traumatic brain injury, antidepressants

PL03-02

MODELING CHRONIC COGNITIVE DYSFUNCTION AFTER TBI: WHERE DO WE GO FROM HERE?

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The long-term consequences of traumatic brain injury can be devastating. While many patients exhibit considerable recovery of many symptoms, a significant subset go on to develop chronic cognitive impairments. These impairments span many modalities, including poor decision-making, limited attention, impulse control problems, reduced working memory and more. Additionally, recent studies have begun to link TBI with numerous psychiatric disorders suggesting that, for some patients, these symptoms may be prodromal to psychiatric conditions. In order for therapeutic agents to appropriately target many of these symptoms, we need to be able to effectively model these in animals. This presentation will discuss recent developments in cognitive-behavioral assessment for experimental TBI. Specifically, I will discuss data covering simple domains of functioning such as cue discrimination to more complex functions such as attention and impulsivity, as well as the implications of these behavioral changes as they apply to modeling psychiatric conditions in rodent models. Over the last several years, the field of experimental TBI has shown large advancements in numerous domains such as injury modeling, biomarker measurements and imaging ability. In order to progress as a field, we also need to implement improved behavioral assessments. This will improve our understanding of the cognitive consequences of brain injury in animal models and be more effective for the assessment of therapeutic agents.

PL03-03

EXECUTIVE FUNCTION AFTER TRAUMATIC BRAIN INJURY: CHALLENGES IN ITS ASSESSMENT & MANAGEMENT

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Executive dysfunction provides one of the most common and debilitating features of traumatic brain injury (TBI), often leading to disability in the home, school, and workplace. While trained clinicians are often able to recognize the behavioral features of executive dysfunction over the course of their management of patients with TBI, many challenges remain in our ability to measure and track these behaviors in an accurate and effective manner. The goal of this presentation is to conduct an evidence-based review of the methods currently available for clinical assessment and treatment of executive dysfunction in TBI patients. This will include a critical analysis of the psychometric properties of instruments currently marketed as neuropsychological tests of executive functions in addition to an update on the empirical support for the most commonly used intervention strategies. The review will also address many of the continuing obstacles that remain in our ability to measure the impact of executive dysfunction across the entire spectrum of TBI.

Keywords: Neuropsychology, Executive Functions, Frontal Lobe, Assessment

PL04 Patient Perspective

PL04-01

DOES THIS WHEELCHAIR MAKE MY BUTT LOOK BIG?

Briana Walker-Tavano
Briana Walker-Tavano Intl., Speaker and Writer, Temecula, USA

On a bright, sunny Sunday afternoon Briana Walker was driving on the freeway when she fainted at the wheel, hitting a cement median at 75 miles per hour. A young, aspiring dancer, just 23 years old at the time of her accident, Briana was determined to reinvent an amazing life in spite of her new and challenging circumstances.

One year after her accident Briana became the first female ever to be featured on the cover of Mobility Management magazine. Shortly thereafter Briana became the Krypto Girl for Colours Wheelchairs. Her images have now been used globally on buses and billboards to change the face of disability.

After meeting another Colours' model, a pioneer in the hip hop world, Briana learned to transform her wheelchair into a dance prop, and together they created one of the first ever wheelchair, hip hop

dance teams to take the national spotlight doing a routine with music sensation Ludacris. In 2007 Briana became the new spokesperson for Overstock.com. Her television commercials and print ads have been seen around the world.

In 2014 she graduated Cum Laude from California State University San Marcos with a Bachelor of Arts in Criminology and Justice Studies. In that same year Briana married and embraces the life of an unconventional homemaker.

Briana wrote her incredible first book, *Dance Anyway,* to help others overcome life's obstacles. She is currently working on her second book about humorous anecdotes when faced with adversity. Some of her humorous stories can be found on her blog *High Heels and Wheelchair Wheels.* Recently, Briana became an advisory board member for *The Hub* magazine and is a part time column writer for the magazine as well.

Briana is currently speaking to people all over the country sharing her contagious and inspiring courage with thousands - teaching everyone the principle - no matter what life throws at you – you can choose to *dance anyway!*

Keywords: Perseverance, Personal Attitude, Overcoming Adversity, Courage, Goal Setting, Humorous Anecdotes

PL04-02

RECOVERY FROM SEVERE TBI: PATIENT PERSPECTIVE

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We present the story of a young woman that sustained severe TBI after being struck by a vehicle while jogging. We review her complicated clinical course, which included multiple operations and intravascular therapies for vasospasm. After a brief clinical presentation by her treating neurosurgeon, the patient will discuss her personal journey of survival, rehabilitation, and recovery.

Keywords: TBI, vasospasm, neurocritical care, rehabilitation

PL05 Neuroimaging of Chronic Traumatic Encephalopathy

PL05-01

NEUROIMAGING CORRELATES OF REPETITIVE LOW-LEVEL BLAST EXPOSURE IN MILITARY SERVICE MEMBERS

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Military service members may undergo blast exposure in a variety of settings, ranging from occupational, repetitive low level exposure to higher levels associated with a traumatic event. Concern exists that traumatic brain injury (TBI) may result from repetitive, low-level blast exposure that occurs in an occupational setting. The current presentation will review studies conducted to date on dynamic entry personnel/breachers, with varying lifetime exposures to blast, with an emphasis on neuroimaging observations.

Dynamic entry personnel have undergone neuroimaging assessments in three distinct studies to date, including: (i) students and instructors at the Dynamic Entry School in Quantico, Virginia, (ii) special operations personnel from the New Zealand Defence Force in Auckland, New Zealand, and (iii) experienced breachers from multiple United States locations, assessed at the National Institutes of Health Clinical Center. Across these studies, diffusion tensor imaging (DTI) and 3D-T1 weighted sequences were acquired for white and gray matter analyses. Advanced Normalization Tools (ANTs) was used for subject processing. White matter labels were provided by the JHU tractography atlas. Cortical thickness maps were generated using ANTs pipeline. ROI-based regression analysis was employed using ANTsR-a data analysis interface between the statistical project R and ANTs. Student t-tests were performed between groups using multiple testing FDR correction. Similar analyses were carried out for cortical thickness maps. Changes in cortical thickness and DTI measures were seen across conducted studies with decreasing cortical thickness measures and white matter fractional anisotropy values observed that were correlated with length of service and independent of age-related changes. Personnel trained to perform breaching maneuvers may be exposed to hundreds of blast events during their career. Ongoing studies will continue to assess whether cumulative changes are seen in the brains of individuals with occupational repetitive low-level blast exposure and will seek to understand the clinical significance of observed differences.

Acknowledgements

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Keywords: neuroimaging, diffusion tensor imaging, blast, military, subconcussive

PL05-02

NEUROIMAGING OF BOXERS

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Traditional structural neuroimaging such computed tomography (CT) and magnetic resonance imaging (MRI) utilized to assess chronic brain injury in boxers typically demonstrate non-specific changes including diffuse atrophy, ventricular dilatation, cavum septum pellucidum (CSP) and white matter changes. Volumetric MRI has been noted to reveal lower brain volumes, in particular involving the amygdala, caudate and thalamus. Diffusion tensor imaging (DTI) has identified decreased fractional anisotropy (FA) in the corpus callosum and internal capsule consistent with decreased white matter tract integrity. Functional neuroimaging may also be useful in identifying neuroradiological evidence of chronic exposure to repetitive trauma. Single photon emission computed tomography (SPECT) scanning may demonstrate decreased perfusion primarily in the frontal and temporal lobes. Qualitative analysis of glucose positron emission tomography (PET) scans may reveal hypometabolism in the bilateral medial temporal and parietal lobes similar to the abnormalities recognized in Alzheimer's disease (AD). Quantitative analysis of these scans has noted decreased glucose metabolism in the bilateral posterior parietal lobes extending to the occipital lobes, bilateral frontal lobes and bilateral cerebellar hemispheres. Furthermore glucose hypometabolism has been reported in the posterior cingulate, another finding consistent with what is observed in AD. Molecular neuroimaging such as amyloid and tau PET scans may hold promise in the future in identifying athletes with chronic traumatic brain injury. Alzheimer's disease.

Keywords: Chronic traumatic brain injury, Alzheimer's disease, Positron emission tomography (PET), Magnetic resonance imaging (MRI),

PL05-03

THE NEUROANATOMY OF CTE

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Chronic traumatic encephalopathy (CTE) is a neurodegenerative disorder associated with repetitive head trauma. Most instances of CTE occur as a result of mild traumatic brain injuries (TBI) in athlete populations. Recently, CTE has also been associated with blast-induced injuries in military personnel and other forms of neurotrauma. Pathologically, CTE is characterized by the deposition of hyperphosphorylated tau (p-tau) protein in neurofibrillary tangles, astrocytic tangles, and neurites in the neocortex and the superficial layers of the medial temporal lobe, diencephalon, and brainstem. The definitive diagnosis of CTE can only be determined at autopsy. However, recent advancements in magnetic resonance imaging (MRI) and positron emission tomography (PET) have significantly aided in the diagnosis of CTE and are crucial in distinguishing CTE from other forms of neurodegeneration, such as Alzheimer's disease. PET tracers for biomarkers such as p-tau and inflammation are in early experimental stages and are currently being used to help confirm the diagnosis of CTE in living research participants. We have recently used such modalities to diagnose and distinguish CTE from AD in an NFL player with a history multiple concussions, and in a patient with frontotemporal dementia and a single, severe TBI. It is apparent that *in vivo* biomarkers and neuroimaging techniques hold promise for developing an *in vivo* diagnostic technique for CTE and could help identify preventative and therapeutic targets.

Keywords: Chronic traumatic brain injury, phosphorylated tau, magnetic resonance imaging (MRI), positron emission tomography (PET, Alzheimer's disease

PL06 Cell Death Is Still Alive

PL06-01

AUTOPHAGY AND NEURODEGENERATION

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Autophagy is a conserved lysosomal degradative process to recycle and eliminate damaged or unused cellular components, including organelles, protein aggregates and lipids. These substrates reach lysosomes by several distinct mechanisms, including selective translocation across the lysosomal membrane known as Chaperone-mediated autophagy (CMA). This cellular process is essential for neuronal homeostasis, and its dysfunction has been directly linked to a growing number of neurodegenerative disorders. Autophagy has been shown to be affected at different steps depending on the neurodegenerative disorder. A proper characterization of the molecular players affected in the autophagic process in the different disorders could be key to determine rate of progress of the pathologies and will be essential for developing targeted therapeutic approaches for each disease based on modulation of autophagy. In this talk, I will provide an overview of the role of autophagy in neurodegenerative diseases, with particular focus on selective forms of autophagy and discuss possible novel future therapeutic approaches based on the repair of the lysosomal system in the affected neurons.

Keywords: Autophagy, Chaperone-mediated autophagy

PL06-02

HEAVY METAL KILLS: ZINC IS AN ENDOGENOUS SUPPRESSOR OF CELL SURVIVAL AND AXON REGENERATION AFTER OPTIC NERVE INJURY

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Like other CNS pathways, the optic nerve cannot regenerate if injured, causing lifelong losses in vision. We recently showed that retinal ganglion cells (RGCs), the projection neurons of the eye, can be induced to regenerate damaged axons back to the brain by combining intraocular inflammation (to elevate levels of the growth factor oncomodulin), a cAMP analog, and *pten* gene deletion. Under these conditions, some RGCs reconnect to appropriate target areas in the brain and restore simple visual responses. However, most RGCs continue to die and only 10% of surviving RGCs regenerate their axons. Because Zn^{2+} has been implicated in cell death in other systems, we investigated its possible role here. Both autometallography and the fluorescent zinc sensor Zinpyr-1 revealed a dramatic increase in free Zn^{2+} in amacrine cell synapses onto RGC dendrites within hours of nerve injury and a delayed transfer to RGCs themselves. Presynaptic Zn^{2+} accumulation requires nitric oxide production via NOS1 and the vesicular zinc transporter protein ZnT3. Chelating Zn^{2+} using TPEN or ZX1, or deleting the gene for ZnT3 (*slc30a3*), reduces Zn^{2+} in amacrine cell terminals and within RGCs and leads to enduring RGC survival. Unexpectedly, these treatments also induce extensive axon regeneration. Thus, Zn^{2+} is a major suppressor of optic nerve regeneration. It will be important to investigate whether Zn^{2+} chelators also promote regeneration after other types of CNS injury.

Keywords: zinc, retina, optic nerve, synaptic, axon regeneration, retrograde signaling

PL06-03

TARGETING THE HOMEOSTATIC ARM OF THE ER STRESS PATHWAY IMPROVES FUNCTIONAL RECOVERY AFTER SCI

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Activation of the endoplasmic reticulum (ER) stress response (ERSR) is involved in the pathogenesis of numerous CNS myelin abnormalities, yet its role in traumatic spinal cord injury (SCI)-induced demyelination is not known. ERSR is activated to maintain protein homeostasis in the ER in response to distinct cellular insults including hypoxia, ischemia, trauma and oxidative damage. Mammalian ERSR includes three signal-transduction pathways initiated by ER stress-sensing proteins: protein kinase RNA-like ER kinase (PERK), inositol-requiring protein-1 (IRE1), and activating transcription factor-6 (ATF6). PERK activation leads to the phosphorylation of the eukaryotic initiation factor 2α (eIF2α) and selective translation of ATF4 and CCAAT/enhancer binding homologous protein (CHOP). Recently, we showed significant improvement in hindlimb locomotion in $CHOP^{-/-}$ mice with thoracic contusive SCI. Parallel pharmacological studies using salubrinal (a selective inhibitor of cellular complexes that dephosphorylate eukaryotic translation initiation factor 2 subunit α) demonstrated a significant improvement in locomotion using basso mouse scale scores. Gait analysis showed significant increase in

maximum speed of coordinated walking and decrease in rear stance and stride length indicating enhanced balance, coordination and plantar placement in animals treated with salubrinal. This improved functional recovery in $CHOP^{-/-}$- and salubrinal-treated mice correlated with an increase in white matter sparing, MBP, claudin 11, Olig2 mRNA levels and decreased oligodendrocyte apoptosis. In contrast, genetic ablation of GADD34 (a stress-inducible signaling effector downstream of CHOP that dephosphorylates eIF2α) or its pharmacological targeting using guanabenz protected mOPCs against ER stress-mediated cytotoxicity and resulted in differential ERSR attenuation after SCI, but there was no improvement in hindlimb locomotor function. Deletion of ATF6 arm of the ERSR failed to improve locomotion after SCI. Thus, the ERSR contributes to oligodendrocyte loss and implicates the critical role of homeostatic arm of the ERSR after SCI. We contend that pharmacological targeting of the ERSR after CNS trauma is therapeutically viable.

Keywords: ER stress, oligodendrocytes, spinal cord injury, white matter sparing

PL07 Facilitating Transparency in Data Analysis for TBI and SCI Research

PL07-01

INTRODUCTION ABOUT BIG AND SMALL DATA IN TBI AND SCI

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Vast amount and highly heterogeneous data describing various aspects of Spinal Cord Injury (SCI) and Traumatic Brain Injury (TBI) have been generated over the last several decades and growing every day. However the next step, generating knowledge from existing data has been hindered by different issues including various heterogeneities, such as differences in outcome measures, data formats, etc. In addition, we currently do not have the ability to analyze and interpret our new data in the context of existing data. The current gap between clinical and experimental outcome measures, time points, etc. also needs to be addressed. The proposed session is aimed to discuss some of these critical issues.

Keywords: data transparency

PL07-02

TOWARDS A ROADMAP FOR TRANSLATION OF CANDIDATE TREATMENTS FOR SPINAL CORD INJURY

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A roadmap for the translation of candidate treatments for spinal cord injury does not exist, effective treatments for human SCI are still lacking, and clinical trials have been initiated with variable amounts of preclinical supporting data. Over the past years we attempted to garner the opinions of researchers, clinicians and consumers regarding the necessary/desirable preclinical data required to justify the execution of a clinical trial – including our most recent opinion polling and discussion on the need of large animals and primate data. Excerpts of these discussions will be presented.

Keywords: translational roadmap, opinion polling, preclinical evidence

PL07-03

PRECLINICAL TRAUMATIC BRAIN INJURY COMMON DATA ELEMENTS: TOWARDS A COMMON LANGUAGE ACROSS LABORATORIES

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Traumatic brain injury (TBI) is a major public health issue exacting a substantial personal and economic burden globally. With the advent of ''big data'' approaches to understanding complex systems, there is the potential to greatly accelerate knowledge about mechanisms of injury, and how to detect and modify them to improve patient outcomes. High quality, well-defined data are critical to the success of bioinformatics platforms and a data dictionary of ''common data elements'' (CDEs), as well as ''unique data elements'' has been created for clinical TBI research. However, there is no data dictionary for preclinical TBI research despite similar opportunities to accelerate knowledge. To address this gap, a committee of experts was tasked with creating a defined set of data elements to further collaboration across laboratories and enable the merging of data for meta-analysis. The CDEs were subdivided into a *Core* module for data elements relevant to most, if not all, studies, and *Injury-Model-Specific* modules for non-generalizable data elements. The goals are to provide a common vehicle to deposit data from the preclinical TBI as CDEs and to facilitate a common language for comparisons across laboratories.

Keywords: Modeling

PL07-04

FACILITATING REPRODUCIBILITY AND DATA INTEGRATION FOR SCI RESEARCH WITH MIASCI AND REGENBASE

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The lack of reproducibility in many areas of science, including spinal cord injury (SCI) research, is due in part to the lack of common reporting standards. Over the past three years an ad hoc consortium of scientists has developed a minimum information reporting standard for SCI experiments, called Minimum Information About an SCI Experiment (MIASCI, J Neurotrauma. 2014 Jul 11. PMID: 24870067). The latest version of MIASCI contains 13 sections: investigator, organism, surgery, perturbagen, cell transplantation, biomaterials, histology, immunohistochemistry, imaging, behavior, biochemistry, molecular biology, and data analysis and statistics. For each of these sections, MIASCI enables scientists to capture essential metadata about the study design, materials and methods. The purpose of MIASCI is to improve transparency of reporting and to encourage the use of best practices. A secondary benefit is to facilitate the aggregation and automated interrogation of diverse datasets using a formal standard language. Thus, a parallel effort is underway to develop an ontology about SCI: the RegenBase ontology. Expanding RegenBase by incorporating MIASCI concepts facilitates paper curation and knowledge creation. We will present MIASCI concepts, show integration with the RegenBase Ontology and briefly describe recent work using MIASCI to annotate published papers studying the effect of kinase inhibitors on SCI recovery.

Acknowledgments

NINDS NS080145 and NICHD HD057632

Keywords: ontology, database, reporting standard, informatics, reproducibility

S01 Clinically Relevant Models of Neuroinflammation after TBI

S01-01

NEUROINFLAMMATION IN THE DEVELOPING BRAIN AFTER INJURY

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Inflammation in the central nervous system, mediated by activated microglia and astrocytes, is implicated in the development of several neurologic disorders in both children and adults. Microglial function is unique in the immature brain due to its role in normal development related to white matter development and synaptic pruning. Microglia are found in large numbers in the white matter tracts early in childhood and move to the cortex later in life. Activation of glia during vulnerable periods in development due to an insult/injury may lead to an exaggerated inflammatory response that can result in ongoing injury and chronic immune dysregulation. Strategies to target microglia/astrocytes and treat neuroinflammation can potentially not only slow disease progression, but also promote repair and regeneration, enabling normal development and maturation of the brain. We have previously demonstrated that intravenous administration of a dendrimer-drug nanoparticle system selectively targets and accumulates in activated microglia in the brain of newborn rabbits with neuroinflammation and CP, resulting in significant improvement in motor function and myelination, attenuation of activated microglia, and decrease in neuronal injury by 5 days. A better understanding of the role and timing of the neuroinflammatory response in the immature brain after TBI is crucial for targeting appropriate dendrimer-drug to activated microglia for modulating the immune response.

Keywords: Microglia, Nanotechnology, Pediatric TBI, Dendrimer

S01-02

FRONTAL LOBE INJURY AND HIGHER-ORDER COGNITIVE FUNCTIONS.

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Preclinical models of the psychiatric complications resulting from TBI are urgently needed to facilitate the development of effective therapeutics. The frontal cortex is heavily implicated in many of the disorders that manifest after TBI, including major depression, bipolar disorder and impulsive aggression, and is often damaged by the impact. We therefore aimed to determine the effects of TBI targeting the frontal cortex (fTBI) in rats using a cognitive behavioral test commonly used to model psychiatric symptoms. 30 male Long Evans rats were trained to perform the five-choice serial reaction time task, in which subjects respond to the brief presentation of a cue light in one of five distinct apertures in order to earn sugar reward. This paradigm is highly sensitive to frontal cortex damage, and provides well-validated measures of visuospatial attention, motivation and motor impulsivity. We then used the controlled cortical impact (CCI) method to induce different severities of fTBI, from severe to moderate ($\sim$50% of severe impact) and milder CCI ($\sim$10% of severe impact). fTBI decreased accuracy of target detection and increased motor impulsivity. Although each severely injured animal continued to show substantive impairments across all measures, 65% of animals that received a mild fTBI, and 35% of those in the moderate fTBI group, showed dramatic improvements in accuracy over 3 weeks to within 15% of their premorbid baseline. In contrast, the performance of non-recovered animals overlapped with that observed following severe fTBI, despite receiving only a mild or moderate injury. Ex vivo analysis of cytokine expression revealed strong correlations between levels of IL-6 and IL-10 with lesion size, and the size of the lesion was also a good predictor of the level of cognitive impairment. However, levels of IL-12 significantly correlated with levels of impulsivity and inattention independent of lesion size, suggesting that this immune signaling molecule may be contributing to cognitive impairment via a unique and potentially druggable pathway. Establishing this model in rats opens up the possibility for research into biomarkers predictive of cognitive recovery or impairment.

Keywords: impulsivity, attention, cytokine

S01-03

TREATMENTS TO TARGET NEUROINFLAMMATION

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Traumatic brain injury (TBI) is now recognized as a chronic injury with multiple secondary cell death events, including neuroinflammation. I discuss here two novel concepts of neuroinflammation-based therapies in TBI. First, exogenous stem cells form ''biobridges'' that facilitate the proper migration of endogenous stem cells from the neurogenic niche to the site of injury following the controlled cortical impact model of TBI in adult rats. Such exogenous stem cell-paved biobridges are enriched with extracellular matrix (ECM) stabilizing the structure and organization to the injured tissues and also guiding the migration of and intercellular communication with the endogenous stem cells. Our results indicate that the injured brain not only presents with abnormal composition and structure of the ECM that contributes to the failure of directed endogenous cell migration towards the injured site, but that TBI-mediated disruption of ECM amplifies neuroinflammation ultimately hindering the homing of endogenous stem cells to the damaged tissue. Accordingly, treatments such as

the formation of biobridges designed to stabilize the ECM structure and to harness the ECM's ability to dampen neuroinflammation stand as potent TBI therapeutics. Second, we advance a novel mechanism of ''nuclear sequestration of inflammatory cell death signals'' (i.e., withholding cell death signals in the nucleus to inhibit their propagation to the cytoplasm), which could potentially enhance cell survival and rescue damaged cells in the TBI brain. The transit of large proteins (>42kD) through the nuclear pore requires carrier proteins, with Exportin 1 (XPO1) identified as a major carrier protein and recently shown to be dramatically upregulated in neural cells juxtaposed to inflammatory cells following TBI. In collaboration with Karyopharm Therapeutics, we demonstrated that a novel class of potent, small molecule, brain penetrating inhibitors of XPO1, termed Selective Inhibitor of Nuclear Export (SINE) compounds, can sequester cell surviving signals (e.g., FOXP1, AKT), as well as cell death signals (NFkB) within the nucleus after TBI, resulting in reduced inflammation and improved behavioral recovery in SINE-treated TBI animals. Altogether, stabilizing the ECM and fostering nuclear sequestration of cell death signals pose as innovative anti- inflammatory response in TBI.

Keywords: Inflammation, Neurotransplantation, Regeneration & Plasticity, Cell Death, Stem Cells, Small Molecules

S02 AGE and SCI

S02-01

FORTY YEARS OF LIVING WITH SPINAL CORD INJURY - PHYSICAL AND PSYCHOSOCIAL CHANGES OVER TIME

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With improved survival and life expectancy, clinicians are facing not only the anticipated conditions that accompany aging with spinal cord injury (SCI), but also must address the more common conditions associated with normal human aging. Individuals aging with SCI have a thinner margin of health, the potential earlier onset of additional chronic conditions, and face the risk of experiencing more severe consequences of those conditions before appropriate medical intervention is sought. The findings from a longitudinal study of aging with SCI conducted in the United Kingdom demonstrate a variety of physical and psychosocial changes experienced by a group of individuals injured prior to 1971. Key themes of importance to clinicians have been identified, including the physical, practical and emotional impact of the process of aging with SCI. Physical changes over the study period of 20 years (1990–2010) focus on cardiovascular risk factors, bowel and bladder changes and skin integrity. From a psychological perspective, the changing patterns of life satisfaction, perceived stress, depressive symptomatology and global quality of life reported by the study participants are described. Finally, changes over time in community participation as well as the participants' perceptions of environmental barriers and facilitators that they experience are discussed.

Keywords: secondary health conditions, psychosocial issues

S02-02

MUSCLE CHANGES WITH SPINAL CORD INJURY AND AGE

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Muscle strength varies widely after human spinal cord injury (SCI). For muscles innervated from the lesion epicenter, evoked forces range from zero (complete muscle denervation) up to usual muscle strength. Age at SCI matters – muscles are stronger when SCI occurs at a younger age (<25 years). The mechanisms contributing to these changes in muscle strength remain unclear. Motoneuron death is common after SCI, but is younger spinal cord more resilient to trauma? Do more motoneurons survive in younger individuals? Are the axons of surviving motoneurons better able to sprout to innervate more muscle fibers? All of these processes would facilitate muscle strength. This trauma has consequential and long-term effects on musculoskeletal biology. In daily tasks, muscles weakened by SCI are inescapably overused. Does chronic overuse predispose motoneurons to death? If so, this may contribute to the new muscle weakness and fatigue reported when individuals with SCI reach 40–45 years. Further, remediating motoneuron death by neuron transplantation may restore muscle innervation and allow use of patterned electrical stimulation of neurons to restore function. But what role does transplant age or aging itself play in functional restoration? These issues will be explored because of their long term impact on function.

Keywords: muscle weakness, motoneuron death, chronic overuse, aging, muscle innervation, neuron transplantation

S02-03

ACCELERATED AGING AFTER SCI

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Clinicians and Researchers who treat and study persons with spinal cord injury (SCI) generally believe that people with SCI 'age' faster than the non-disabled population. The core evidence for this 'accelerated' or 'premature' aging is the earlier onset of 'chronic diseases'; the greater prevalence of chronic diseases; and the greater mortality rate and reduced lifespan of persons with SCI. Impairments of body structures and functions due to the SCI as well as the increased stressors of living with SCI are suspected to be the drivers of 'accelerated' aging. The biological processes underlying and indexing the clinical evidence have yet to be quantified. This presentation will review the evidence supporting the theory of 'accelerated' aging of persons with SCI, identify factors that may 'drive' the accelerated aging process, and present the proposed cellular & molecular hallmarks of aging.

Keywords: Aging, SCI

S03 Novel and Emerging Imaging for Detection and Diagnosis of TBI

S03-01

MAGNETIC RESONANCE IMAGING OF MILD TRAUMATIC BRAIN INJURY

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There has been a sea change regarding the potential physiological consequences of mild traumatic brain injury (mTBI) over the past 5–10 years.

It was initially believed that mTBI resulted in limited behavioral and no long-term neurological consequences, except for in a small percentage of patients with pre-existing psychiatric conditions. More recently, a proliferation of neuroimaging studies have reported that neuronal pathology may be present long after traditional outcome measures (e.g., balance and neuropsychological testing) have returned to pre-morbid levels of functioning. Animal models suggest that there are several different mechanisms, as well as interactions between mechanisms, through which head trauma can affect neural functioning. For example, trauma can directly affect neuronal function (e.g., alterations in synchronous excitatory neuronal activity), cerebral metabolism and the associated coupling with cerebral blood flow, glutamate levels, the energetic needs of cells following neurotransmission, the structural integrity of white matter matter/microvasculature, and the intracellular/extracellular matrix. The current talk will focus on the use of magnetic resonance imaging (MRI) techniques to investigate some of these neuropathologies across the spectrum of mTBI disorders. Specifically, the talk will include a review of recent MRI findings in single-episode and repetitive mTBI, a discussion of how trauma may affect underlying signals of interest, as well as several methodological challenges associated with the analyses of mTBI patients. We conclude that the heterogeneity inherently associated with mTBI research demonstrates the need for well-powered clinical studies in homogeneous samples (time post-injury, injury severity, single versus repetitive mTBI, chronically symptomatic versus asymptomatic, etc.) and novel analytical techniques. Studies that incorporate multiple MRI modalities are critically needed to truly understand the underlying pathophysiology and natural course of recovery in mTBI.

Keywords: mild, traumatic brain injury, magnetic resonance imaging, connectivity, neurobehavioral symptoms

S03-02

MRI OF EXPERIMENTAL TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) is a leading cause of death and disability. The initial physical impact of TBI causes direct mechanical damage and is followed by progressive secondary responses, including disruptions of cerebral blood flow (CBF) and vascular reactivity (VR), which could lead to metabolic stress, vascular dysfunction, neural dysfunction, and ischemia. In rat models of mild to moderate TBI, we observed dynamic and widespread abnormalities of CBF and VR in and around the impact area 1–3 hours after injury. Importantly, many brain regions with disrupted CBF and VR were not yet abnormal on anatomical and diffusion MRI at this time point. These observations suggest that CBF and VR are more sensitive to acute TBI and may have predictive value.

In addition, calcium dysfunction is involved in secondary traumatic brain injury (TBI). Manganese-enhanced MRI (MEMRI), in which the manganese ion acts as a calcium analog and a MRI contrast agent, was used to study rats subjected to a controlled cortical impact. Comparisons were made with conventional T_2 MRI, sensorimotor behavior, and immunohistology. We concluded that MEMRI detected early excitotoxic injury in the hyperacute phase, preceding vasogenic edema. In the subacute phase, MEMRI detected contrast consistent with tissue cavitation and reactive gliosis. MEMRI offers novel contrasts of biological processes that complement conventional MRI in TBI. http://ric.uthscsa.edu/duong/index.htm

Keywords: MRI, cerebral blood flow, diffusion tensor imaging, manganese enhanced MRI, control cortical impact, animal model of TBI

S03-03

CLINICAL PHENOTYPE OF TRAUMATIC VASCULAR INJURY AND POSSIBLE THERAPEUTIC IMPLICATIONS

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Traumatic Vascular Injury (TVI) is a well-established but relatively understudied endophenotype of TBI. Studies in humans with moderate to severe TBI, as well as from athletes and military Veterans exposed to repetitive mild TBIs, demonstrate prominent microvascular pathology. TVI is an attractive target for therapeutic intervention, as there are multiple well established pharmacologic and non-pharmacologic therapies which target vascular health. Pharmacologic therapies targeted at improving cerebrovascular function such HMG-CoA reductase inhibitors, phosphodiesterase 5 (PDE5) inhibitors, HDL mimetics, and PPAR-g agonists, among others, have been studied in TBI models and many are approved for human use in other diseases. Non-pharmacologic therapies targeted at improving vascular function, including aerobic exercise, dietary interventions, and nutraceuticals such as omega-3 fatty acids, also show promise for limiting neural injury and promoting plasticity and repair after TBI. Early-phase clinical trials of TVI-directed therapies will require well-validated biomarkers which can be used to document target engagement and to provide evidence of biological efficacy. MRI is a promising tool to measure cerebrovascular reactivity non-invasively, as well as to assess disruption of the blood-brain barrier. Near InfraRed Spectroscopy (NIRS) also shows promise as an inexpensive and widely available biomarker of TVI. We have used MRI and NIRS with a hypercapnia challenge to demonstrate that CVR is commonly depressed after TBI. Further, CVR shows promise as a pharmacodynamic biomarker for TVI-directed therapies.

Keywords: cerebrovascular reactivity, PDE5 inhibitors, arterial spin labelling, dynamic contrast enhancement

S04 Progenitor Cell Therapy for Adult TBI: Preclinical Findings and Clinical Outcomes

S04-01

CELLULAR THERAPIES FOR TBI: TARGETS AND APPROACH

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Currently there are no approved small molecule or biological therapeutic to mitigate the secondary neuroinflammatory response that ensues after severe traumatic brain injury. Our group has focused on the use of progenitor cell therapeutics to mitigate the inflammation and subsequent edema associated with TBI. Pre-clinical data using autologous bone marrow derived mononuclear cells suggest that the observed functional improvements noted in rodent models is related to the polarization of microglia and macrophages to a M2 phenotype vs. a M1 phenotype. Phase 1 and Phase 2 clinical trials in adults and children have focused on the anti-inflammatory effects and associated structural preservation that can be quantified using DT-MRI volumetrics and tractography. Importantly, these imaging data can be correlated with functional outcomes when examining discrete regions of interest. The data to be presented will review our early phase clinical trials and the results that correlate imaging findings and outcomes associated with cellular therapies for severe TBI.

Keywords: Cell Therapy

S04-02

PRECLINICAL MODELS OF CELLULAR THERAPY: INFLAMMATORY RESPONSE

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Objective: The proinflammatory environment after TBI leads to breakdown of the blood-brain barrier (BBB) thereby worsening neurologic and cognitive deficits. We have previously shown that intravenous administration of adult bone-marrow-derived stem cells can reduce BBB permeability and this protective effect requires an intake spleen. Recent studies have implicated vagus nerve regulation of splenic alpha7 nicotinic receptor signaling in the regulation of systemic inflammation. However, it is not known if this mechanism plays a role in TBI-triggered inflammation and BBB breakdown.

Method: Animals received controlled cortical impact injury and were treated with various agents. Cytokine levels were measured by ELISAs and blood-brain barrier permeability by Evans blue extravasation.

Results: Using pharmacological and genetic approaches, we have observed that blockade of alpha7 signaling exacerbates, while its activation attenuates inflammation and TBI-triggered BBB permeability. To test the translation usefulness of our findings, we tested the efficacy of galantamine administration. Post-injury intraperitoneal administration of galantamine reduced BBB permeability and improved outcome.

Conclusion: Stimulation of nicotinic alpha7 receptors reduces inflammation and BBB permeability after experimental TBI. These results support the translational relevance of our findings.

Keywords: nicotinic alpha7 receptor, vagus nerve, spleen, galantamine

S04-03

NEUROIMAGING AND FUNCTIONAL OUTCOMES AFTER CELLULAR THERAPY FOR SEVERE ADULT TBI

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Despite numerous clinical trials, no pharmacotherapeutic interventions have been shown to improve patient outcomes following severe traumatic brain injury (TBI) in children or adults. We report longitudinal clinical outcome data in adults with severe TBI enrolled in a dose escalation trial examining impact of intravenous infusion of bone marrow mononuclear cells (BMMNC). Neuroimaging and neuropsychological outcomes were evaluated 1 and 6 months after injury in three cohorts of five patients and a non-treated control cohort of patients with Glasgow Coma Scale scores of 5 to 8.

Secondary aims of the trial examined whether BMMNC infusion showed neuroprotective effects characterized by preservation of corpus callosum structure on serial structural neuroimaging studies. Fractional anisotropy from diffusion tensor imaging studies indexed microstructural integrity of the entire corpus callosum. At 1 month after injury, higher fractional anisotropy values were evident across all treated groups. At 6 months after injury, well-preserved fractional anisotropy values were demonstrated in low and middle dose groups.

The impact of BMMNC dose on neuropsychological outcomes was also evaluated 1 and 6 months after injury. Outcome domains included measures of functional, neuropsychological, and psychological health status. The treated and nontreated groups showed improvement from the 1 to 6 month follow-up on the Glasgow Outcome Scale-Extended, Disability Rating Scale, and Mayo-Portland Adaptability Inventory. Glasgow Outcome Scale scores tended to improve in more patients receiving low to mid doses of BMMNC infusion than in nontreated patients.

Long-term functional and cognitive outcomes were significantly related to the integrity of callosal subregions. Six months after injury, fractional anisotropy of the whole corpus callosum was significantly positively correlated with the Glasgow Outcome Scale-Extended and neuropsychological outcomes including processing speed, divided attention, and fine motor speed and negatively correlated with the Mayo-Portland Adaptability Index composite score. Greater preservation of callosal integrity was associated with better functional and neuropsychological scores when assessed at the chronic stage of recovery from severe TBI.

Keywords: diffusion tensor imaging, functional outcome, neuropsychological outcome, corpus callosum

S05 The Role of apoE and APOE Genotype in Outcome after TBI

S05-01

APOE4 AS A RISK FACTOR FOR POOR OUTCOME AFTER TBI - CLINICAL AND PRECLINICAL EVIDENCE

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The apoE protein is an important brain apolipoprotein whose primary function is as a cholesterol transporter. There are 3 apoE isoforms, apoE2, apoE3 and apoE4 – encoded for by polymorphisms in the APOE gene. The APOE4 allele is best known as a genetic risk factor for the development of Alzheimer's disease, but it is also associated with poor outcome after TBI, and may be linked to the development of chronic traumatic encephalopathy in athletes. This talk will critically assess the clinical and preclinical evidence data supporting the link between APOE4 and TBI, and unpublished data from humanized APOE mice will also be presented. This new data will focus on mechanisms by which APOE4 can negatively impact outcome after TBI including through aberrant amyloid clearance, increased neuroinflammation and impaired closure of the blood brain barrier.

Keywords: apoE, amyloid, inflammation

S05-02

THE EFFECTS OF APOE GENOTYPE ON PROTEOMIC AND LIPIDOMIC RESPONSE TO INJURY IN DIFFERENT MOUSE MODELS OF TBI

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Introduction: We have used different laboratory models of TBI and quantitative proteomics and lipidomics approaches to generate brain proteomic and lipidomic profiles and identify cellular mechanisms that are triggered in response to TBI. Moreover, we have carried out these studies in mice transgenic for different isoforms of human APOE in order to discriminate between the cellular mechanisms associated with favorable (APOE3) versus unfavorable (APOE4) outcomes after TBI.

Methods: We used the well characterized controlled cortical impact (CCI) model administered with a moderate (1.3 mm depth) or severe (1.8 mm) single injury in 6–8 month old APOE transgenic mice, and in targeted replacement APOE mice we administered a repetitive mild TBI (r-mTBI) model developed in house (Mouzon *et al.* 2012) with a paradigm of three hits per week for one month. Proteomic and lipidomic analyses employed liquid chromatography-mass spectrometry (LCMS) approaches

with phospholipid analyses against internal standards and protein samples undergoing isobaric tagging for relative and absolute quantitation (iTRAQ). Using Ingenuity Pathway Analysis software, datasets of significantly modulated proteins were mapped onto known molecular relationships to determine the functional significance of the observed changes.

Results: In our CCI model our data identify significant changes in the expression of many proteins in the mouse hippocampus and cortex at 24 hrs, 1 month and 3 months after TBI, including proteins with significantly different modulation in APOE3 compared to APOE4 mice. APOE-dependent lipidomic changes are also evident in our r-mTBI model.

Conclusions: In our different mouse models of TBI our datasets clearly demonstrate APOE dependent responses to injury that may represent targets for therapeutic intervention.

Keywords: lipidomics, proteomics, mild TBI, APOE

S05-03

NEUROPROTECTIVE AND ANTI-INFLAMMATORY THERAPIES FOR CNS INJURY BASED UPON APOLIPOPROTEIN-E

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Humans are the only species to express multiple isoforms of apolipoprotein-E. While best known as a risk factor for Alzheimer's Disease, APOE4 is also a risk factor for worse outcomes following Traumatic Brain Injury (TBI). Compared with apoE2 and apoE3, the apoE4 protein is a very poor anti-inflammatory/neuroprotective/neurotrophic agent. We found that COG112/COG1410, small peptide mimetics of holo-apoE2/3 were potent anti-inflammatory agents in BV2-microglial cultures and primary macrophage cultures from mice with different APOE backgrounds. In collaboration with Laskowitz, Hoane, or James, we found COG1410 to be neuroprotective in closed head injury, controlled cortical impact and intracranial hemorrhage models in rodents. In collaboration with Colton, we also found reduced inflammation, reduced amyloid and neurofibrillary tangle pathologies, and reduced neuronal loss in the CVN model of Alzheimer's upon COG1410 treatment. In each model, behavioral outcomes were significantly improved in COG1410 treated animals versus their control counterparts. In addition to being active when administered 2 hours after trauma, COG1410 also efficiently crossed the blood brain barrier, even in naïve animals. As a Protein Phosphatase 2A activating drug or PAD, COG1410 displays a novel mechanism of action that supports its anti-inflammatory activity and portions of its neuroprotective activity. These and other data support the concept that APOE4/apoE4 is associated with loss of a neuroprotective function in TBI and AD.

Keywords: apolipoprotein-E, trauma, Alzheimer, Protein Phosphatase 2A

S06 Genetic Dissection of Locomotor Circuitry

S06-01

CONDITIONAL SILENCING OF PROPRIOSPINAL NEURONS: HOPPING TO A NEW TUNE

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Locomotor function in the intact animal, and recovery after injury is dependent on spinal cord central pattern generating (CPG) circuitry that produces the flexor/extensor, right/left, hindlimb/forelimb alternating pattern of stereotypic stepping. Long propriospinal neurons that interconnect the two spinal enlargements have been well-defined anatomically, and are presumed to participate in locomotor activity, however, their role in CPG activity remains a mystery. We are investigating the functional contributions of long ascending propriospinal neurons (LAPNs) in the spinal cord using a conditional two viral vector system that allows specific neuron populations to be silenced based solely on their anatomy. Targeted neurons reversibly express enhanced tetanus neurotoxin (eTeNT) which proteolytically cleaves vesicle-associated membrane protein 2, and prevents exocytosis of synaptic vesicles. We have targeted LAPNs with cell bodies at L2 and terminals at C6. Bilateral injections of HiRet-TRE-EGFP.eTeNT at C6 and tetracycline-responsive AAV2-CMV-rtTAV16 at L2 were performed to doubly-infect LAPNs followed by defined periods of *ad libitum* doxycycline (DOX, 15 mg/ml in drinking water) to induce eTeNT expression.

Conditional silencing of the L2-C6 LAPNs induced a symmetrical, rabbit-like gait resulting from the disruption of right/left alternation of both forelimbs and hindlimbs, where both girdles moved in near synchrony. Hopping was characterized by a significant increase in hip height displacement, however there were no overt changes in the flexor/extensor (intralimb) coordination. The phenotype was robust, reversible and repeatable and occurred in all animals silenced. Approximately 25–30% of steps showed a disrupted right-left phase relationship during silencing. Interestingly, hindlimb alternation during swimming, a bipedal mode of locomotion, was not disrupted by silencing the LAPNs. These results suggest that L2-C6 LAPNs are critical components of the CPG circuitry mediating right/left alternation in the intact animal. These data further suggest that current models of locomotor circuitry need to include a half-center responsible for left/right control independent of rhythm generation. Supported by GM103507, NS089324, and KSCHIRT 13-14 (DSKM, SRW).

Keywords: spinal cord, central pattern generator, propriospinal neuron, conditional silencing, locomotion and gait

S06-02

TAKING A STEP TOWARDS MOTOR FUNCTIONAL RECOVERY AFTER SPINAL CORD INJURY: GENETICALLY DEFINING SPINAL MICROCIRCUITS

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Neural circuitry that produces the basic rhythm and pattern of locomotion is situated in the spinal cord. Following spinal cord injury, locomotor training can lead to significant improvement in gait. The mechanisms underlying this neural plasticity are unknown. In this talk, I will discuss how genetic techniques have provided a window through which to study spinal motor circuits and their plasticity. I will first discuss spinal regulation of hand grasp, and then spinal control of walking, outlining a circuit important for recovery of function after injury. Understanding mechanisms of spinal plasticity is important for the further development of strategies aimed at improving motor function following spinal cord injury.

Keywords: locomotion, neural plasticity, grasp, microcircuits

S06-03

MUSCLE SPINDLE FEEDBACK DIRECTS LOCOMOTOR RECOVERY AND CIRCUIT REORGANIZATION AFTER SPINAL CORD INJURY

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Spinal cord injuries alter motor function by disconnecting neural circuits above and below the lesion, rendering sensory inputs a primary

source of direct external excitatory drive to local spinal networks caudal to the injury. Here, we studied mice lacking functional muscle spindle feedback to determine the role of this sensory input in gait control and locomotor recovery after spinal cord injury. High-resolution kinematic analysis of intact mutant mice revealed proficient execution in basic locomotor tasks but poor performance in a precision task. After lateral hemisection injury, wild-type mice spontaneously recovered basic locomotor function, whereas mice with deficient muscle spindle feedback failed to regain control over the ipsi-lesional hindlimb. Virus-mediated tracing demonstrated that mutant mice exhibit defective rearrangements of descending circuits projecting to deprived spinal segments following injury. Our findings revealed an essential role for muscle spindle feedback in directing basic locomotor recovery and facilitating descending circuit reorganization after spinal cord injury.

Keywords: sensory feedback, proprioception, descending detour circuit formation, locomotion

S07 Clinical Science of Sports Concussion

S07-01

EPIDEMIOLOGY OF SPORTS CONCUSSIONS

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Introduction: Concussions are a common sports injury, with an estimated 300,000 reported/recognized and 7–9 times as many unreported/unrecognized sports concussions annually.

Objective: To describe the epidemiology of sports concussion in the US. More specifically to describe concussion rates and clinical patterns by sport, athlete gender, and athlete age.

Design: Descriptive epidemiology study coupling a literature review with review of data captured by several national sports injury surveillance systems including: The National Center for Catastrophic Sports Injury Research, The National Collegiate Athletic Association Injury Surveillance Program, NATA NATION, and High School RIO.

Results: Rates and patterns of injury vary by sport, athlete gender, and athlete age. Concussion rates are highest in full contact sports. In gender comparable sports, females have higher concussion rates than males. Older athletes have higher concussion rates than younger athletes. Concussion rates have risen significantly over the past decade. The vast majority of sports concussions are new injuries rather than recurrences. Although there are some differences by gender and age, most athletes report less than four concussion signs/symptoms upon presentation with headache being the most commonly reported symptom and loss of consciousness rarely reported, most athletes have all concussion symptoms resolve within one week of injury with few athletes experiencing symptoms longer than 3 weeks, and although physicians are now involved in the management of most injured athletes and most injured athletes are now cleared for return to play by a physician, only a small proportion of concussed athletes receive care from a specialist.

Conclusions: The epidemiology of concussion varies by sport, athlete gender, and athlete age. A knowledge of athlete subgroup differences will help clinicians with staffing decisions, with clinical expectations and comparisons, and with evaluation of efforts to prevent sports concussions, to minimize those injuries that do occur, and to improve patient outcomes.

Keywords: epidemiology, sports, gender, age, rates

S07-02

THE CHALLENGES OF CONCUSSION DIAGNOSIS IN ATHLETES

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Previous concussion biomechanics research has relied heavily on the animal model or laboratory reconstruction of concussive injuries captured on video footage. The utility of head impact sensors/accelerometers has received significant attention in recent years. Real-time data collection involves a novel approach to better understanding the medical issues related to sports concussion. Because of the varying magnitudes and locations of impacts resulting in concussion, as well as other factors such as the frequency of sub-concussive impacts and number of prior concussions, it may be difficult to establish a threshold for concussive injury that can be applied to football and other helmeted contact sports such as hockey and lacrosse. As reported previously in the literature, any proposed theoretical injury threshold should be interpreted with caution. Despite this, biomechanics research has still provided us with valuable information for improving safety in sports such as football and hockey. Our findings further substantiate the notion that concussions must be managed using a multifaceted approach The most important findings of these combined studies has been: 1) that concussions can occur at lower impact magnitudes than previously thought; 2) that measures of linear acceleration appear equally important to cause concussion as angular acceleration; 3) that athletes can sustain a high number of head impacts in a season (many exceeding 80–90 g) and never sustain a diagnosed concussion; and 4) clinicians should not attempt to use impact magnitude or location to predict acute clinical outcomes of symptom severity, neuropsychological function, and balance. Our earlier studies, combined with those of several other studies on this topic, call for more research to be conducted to investigate how linear and rotational acceleration relate to measures of symptom severity, neurocognitive function, and postural stability, in larger sample sizes across the entire recovery period. Additionally, the role of this technology should be further investigated to identify its utility for behavior modification and improved player mechanics.

Keywords: biomechanics, head impact, concussion threshold

S07-03

EVIDENCE BASED ASSESSMENT TO SPORT CONCUSSION MANAGEMENT

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This presentation addresses the current state of evidence that supports the valid assessment and management of sport related concussion from youth to the professional ranks. While the interest in sport related concussion has increased substantially over the past decade, the available clinical tools to provide appropriate diagnostic and treatment guidance are in an active state of development. Appropriate management of a concussion requires clinical assessment and treatment methods to be supported by a strong body of evidence to allow for valid and reliable clinical decisions to be made. Key clinical domains in the assessment of concussion are discussed, including cognition, symptom status, and balance/ vestibular/ ocular function. The existing standards for test measurement and critical metrics for valid clinical decisions will be applied to this discussion to provide a framework for the essential evidence necessary for the valid use of tests in a clinical context. Various assessment methods (computer-based, traditional administration) and measurement tools are highlighted with respect to their existing evidence supporting clinical utility across the full age

range. In addition, the current evidence supporting various treatment and management methods of concussion effects is examined, including cognitive restructuring/ reassurance, aerobic therapy, and other therapies. Return to school and activity will also be reviewed. Reference is made to the 2013 American Academy of Neurology Sport Concussion evidence-based guidelines as well as more recent research. Recommendations for future research is provided to address the existing needs.

Keywords: Sport Concussion, Evidence Based, Concussion Assessment, Concussion Management

S08 Operation Brain Trauma Therapy: The Thrill of Victory and the Agony of Defeat

S08-01

MULTI-CENTER PRE-CLINICAL THERAPY SCREENING IN TBI: RESULTS OF THE OBTT CONSORTIUM

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Operation Brain Trauma Therapy (OBTT) is a fully operational, rigorous, and productive multi-center, pre-clinical drug and circulating biomarker screening consortium for the field of traumatic brain injury (TBI). In this presentation, I will synthesize the findings from the first five therapies tested by OBTT, and discuss both the current work that is ongoing and potential future directions. Based on the results generated from the first five therapies tested within the exacting approach used by OBTT, four (nicotinamide, erythropoietin, cyclosporine A, and simvastatin) performed below or well below what was expected based on the published literature. However, OBTT has identified the early post-TBI administration of levetiracetam as a promising agent and has advanced it up the phylogenic scale to a FPI model in micropigs. The 6th and 7th therapies have just completed testing (glibenclamide and Kollidon VA 64) and an 8th drug an aquaporin-4 blocker AER 271 is in testing. The results of those three therapies will also be updated. Given the concerns related to what has been described as a reproducibility crisis in basic and pre-clinical research, and the failures in clinical translation of therapies in TBI, rigorous multi-center, pre-clinical approaches to therapeutic screening such as OBTT may be important for the ultimate translation of therapies to the human condition.

Keywords: consortium, reproducibility, behavior, neuropathology, biomarkers

S08-02

A UNIQUE TOOL FOR CROSS MODEL COMPARISON IN PRECLINICAL TRAUMATIC BRAIN INJURY

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The Operation Brain Trauma Therapy (OBTT) testing platform is comprised of 4 Drug Screening Centers and a Biomarker Core. Candidate TBI therapies are first screened across well-established rodent models of traumatic brain injury (TBI) with the most promising drugs selected for advanced testing in a micropig animal model (VCU). In this presentation, I will give an overview of the OBTT approach to primary drug screening in rodent TBI models to include comparing and contrasting neurobehavioral outcomes specific to each model. The primary OBTT TBI drug screening models include the fluid percussion injury (FPI) model (Miami), the controlled cortical impact (CCI) model (U. Pitt.) and the penetrating ballistic-like brain injury (PBBI) model (WRAIR). In addition, this presentation will illustrate the underlying rationale for combining neurobehavioral outcomes with neuropathological and biomarker measures into a scoring matrix to provide comprehensive top-down vs. bottom-up comparisons on each drug. Importantly, for primary drug screening, unified treatment regimens (tailored to each drug) are employed across all TBI models and animals are randomly assigned to treatment vs. control groups with surgeries, behavioral testing and all subsequent analyses conducted in a blinded fashion within and between each Center. The strength of this approach is that it provides unprecedented rigor to pre-clinical TBI drug research that has been deemed critical for the successful translation of therapies to clinical studies. This project is supported by U.S. Army Grant W81XWH-10-1-0623.

Keywords: TBI, OBTT, Neuroprotection, Biomarkers

S08-03

BIOMARKERS AS A WINDOW ON TBI MODELING AND THERAPEUTIC EFFICACY: RESULTS OF THE OBTT CONSORTIUM

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Operation Brain Trauma Therapy (OBTT) is a multi-center pre-clinical drug screening consortium testing promising therapies for traumatic brain injury (TBI) in 3 well-established TBI models, namely parasagittal fluid percussion injury (FPI), controlled cortical impact (CCI), and penetrating ballistic-like brain injury (PBBI) using state-of-the-art behavioral and histological outcome tools as well as assessing circulating brain damage biomarkers.

In this presentation, I will discuss unique characterization of these models using novel candidate biomarkers [glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase (UCH-L1)] demonstrating that different experimental TBI models display specific biomarker profiles. Furthermore, I will present evidence that drugs differently affect distinct types of lesions as reflected by distinct biomarker pathways that are also associated with diverse functional deficits and pathological consequence in brain tissue. These observations indicate that biomarkers may be a valuable means for characterization, standardization and refinement of TBI animal models, and serve as surrogate markers of treatment effect after a specific therapeutic intervention.

In reviewing these concepts, a series of critical issues such as need for evidence of analytical validity and clinical translation as well as implications for future research and theranostic roles of biomarkers in drug discovery and clinical trials will be discussed.

Keywords: Ubiquitin carboxyl-terminal hydrolase-L1, Glial fibrillary acidic protein, Fluid percussion injury, Controlled cortical impact, Penetrating ballistic-like brain injury, Rat

S09 Influence of Lesion, Stress, and Exercise on Blood Brain Barrier Permeability in the CNS

S09-01

REMOTE BLOOD BRAIN BARRIER DISRUPTION AFTER MID-THORACIC SPINAL CORD INJURY

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Spinal cord injury results in a series of cellular cascades at the injury site which are largely comprised of inflammatory processes. Considerable research has been dedicated to cellular events at the epicenter but little is known about changes in the blood brain barrier remote to the primary injury site. This presentation will discuss the latest evidence showing: 1) the physiological response of the blood brain barrier to exercise; 2) active trafficking of peripheral monocytes into the lumbar spinal cord after mid-thoracic contusion; and 3) passive permeability of the barrier after spinal cord contusion. The role of these changes in promoting an inflammatory microenvironment and the implications for functional recovery will be discussed.

Keywords: Lumbar cord, remote effects, activity-dependent, Lamina 10

S09-02

MICROGLIAL ACTIVATION AND THE RECRUITMENT OF MONOCYTES TO THE CNS: LESSONS LEARNED FROM MODELS OF PSYCHOLOGICAL STRESS AND SCI

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Recruitment of immune cells may be beneficial or detrimental to intrinsic repair processes after CNS injury. Mounting evidence indicates that the activation profile of the resident microglia (M1 or M2) influences the recruitment of immune cells to the CNS. From our work in other models we have gained insight into the dynamics of microglia activation and monocyte recruitment. For instance, repeated social defeat (RSD), a psychological stressor, activates microglia and promotes the recruitment of monocytes to the brain. Following RSD, microglia preferentially secrete chemokines and monocyte recruitment is dependent on chemokine receptor interactions including chemokine receptor-2 and fractalkine receptor. Moreover, monocytes are recruited to specific areas of the brain where microglial activation is robust. The monocytes that are recruited to the brain are inflammatory ($CCR2^{+}$/$CD45^{Hi}$/$Ly6C^{hi}$) and produce high levels of interleukin-1b. Importantly the consequence of this increased recruitment of ''inflammatory'' monocytes to the brain is the development of anxiety-like behavior. Furthermore, the disruption of microglial activation, prevention of monocyte recruitment, or blockade of IL-1b signaling, all ameliorate the stress-induced anxiety. Building on this work, we have also detected selective recruitment of monocytes after SCI. This is associated with an M2a profile of microglia. This active recruitment of monocytes that become ''repair'' macrophages ($IL\text{-}4Ra^{+}$/Arg^{+}), however, is impaired in older mice and is associated with reduced functional recovery after SCI. Overall, data are highlighted from models of stress and SCI that may provide insight into the mechanisms by which microglia help to selectively recruit monocytes to the CNS.

Keywords: Neuroimmunology, Stress, Monocytes, microglia, SCI

S09-03

EXERCISE AFTER TRAUMATIC BRAIN INJURY: IS IT A DOUBLE-EDGED SWORD?

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This talk will focus on challenges implementing exercise after traumatic brain injury. (TBI). Exercise has been proven valuable because it increases proteins that are important in neuronal plasticity and repair. Although exercise helps the brain recover from injury it may impair recovery if it takes place during the early post injury period and is associated with stress. The critical nature of the timing of experience-dependent rehabilitative interventions during different post-traumatic injury periods will be discussed. Stress influences the neuroplasticity and response to rehabilitative interventions. Thus, neuroendoctine responses to brain injury and exercise will also be addressed. The implications of neuroendocrine dysregulation will have an influence on the timing of rehabilitation as well as the return to athletic activities following a concussion. Finally some of the challenges of translating the basic science of concussion and exercise will be discussed.

Keywords: exercise, neuroendocrine, mild TBI, stress

S10 Open Communication: TBI

S10-01

PREVENTING POSTTRAUMATIC EPILEPTOGENESIS BY STIMULATING CORTICAL EXCITATORY ACTIVITY AFTER TRAUMATIC BRAIN INJURY

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Homeostatic synaptic plasticity has been proposed to underlie acquired epileptogenesis. This hypothesis suggests that loss of neuronal activity following brain injury will initiate epileptogenesis while stimulating neuronal activity may prevent it. However, whether stimulating neuronal activity can prevent posttraumatic epileptogenesis has not been directly tested. In the partially isolated neocortex model of posttraumatic epileptogenesis (undercut) in mice, we made patch clamp recording from cortical layer V pyramidal neurons and found that spontaneous action potential firings in these neurons were significantly reduced at both 1 and 7 days after injury. The frequencies of both spontaneous excitatory and inhibitory synaptic currents (sEPSCs and sIPSCs) were also significantly depressed but without significant changes in the amplitudes of these events. In Thy1-channelrhodopsin-2 (ChR2) transgenic mice that express ChR2 in cortical layer V pyramidal neurons, we made undercut injury and applied optogenetic stimulation of the injured cortex using LED light for 7 days *in vivo*. Chronic optogenetic stimulation resulted in increased seizure threshold as indicated by a higher drug dosage required for inducing seizure and a longer latency period in pentylenetetrazol (PTZ) test, and reduced cortical hyperexcitability as indicated by decreases in the percentages of slices and mice in which epileptiform activity could be evoked in field potential recording. The frequencies of both sEPSCs and sIPSCs in neurons after optogenetic stimulation were significantly lower that the control undercut mice. The results support that homeostatic plasticity plays a role in the posttraumatic epileptogenesis and that stimulating activity of cortical excitatory neurons has prophylactic effect on posttraumatic epileptogenesis.

Keywords: Homeostatic plasticity, Optogenetic, Posttraumatic epileptogenesis, Cerebral cortex

S10-02

CHRONIC NEUROPHYSIOLOGICAL RECORDING OF THE HIPPOCAMPUS IN AWAKE BEHAVING SWINE AFTER DIFFUSE BRAIN INJURY

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We have previously established an acute recording methodology to interrogate hippocampal circuitry after diffuse brain injury (DBI) in a swine model of rotational injury. Injuries were administered over a range of coronal rotational accelerations (180260 rad/sec) that induced little or no loss of consciousness (<15 min), yet exhibited axonal pathology. Limitations of electrophysiological recording under anesthesia have led us to develop a chronic hippocampal electrode implantation model in the awake, freely moving swine, allowing examination of hippocampal networks engaged in relevant behavior after injury. Repeated concurrent electrophysiological and behavioral measures enable examination of how network level interactions may be disrupted after DBI. We have developed a stereotaxic surgical technique for precise implantation of a custom 32-channel silicone electrode into the swine hippocampus that allows for recordings of both single units in layer CA1 and dentate, as well as simultaneous laminar field potentials while the animal is awake and freely moving during behavioral tasks. We have also developed a novel object recognition task for swine, a behavior known to be hippocampal dependent. Pigs were trained on this task prior to electrode implantation. Preliminary behavioral results indicate that sham injured swine reliably interact longer with novel objects versus familiar objects. Moreover, we demonstrate robust extracellular field potentials out to 5 months post-implantation, as well as stable unit recordings pre- and post-implantation. Using spectral density analysis we report a prominent peak in hippocampal theta rhythm power in the freely behaving pig with positive shifts in peak frequency and peak power during periods of locomotion. This dominant hippocampal rhythm has previously been shown to be disrupted in rodent traumatic brain injury models. Here we demonstrate the feasibility of combining chronic hippocampal electrophysiological recordings with concurrent behavior in freely moving large animals. Combining this methodology with our established DBI model in pigs may reveal mechanisms of trauma-induced network dysfunction which may lead to innovative neuromodulatory therapies.

Keywords: electrophysiology, behavior, rotational injury, mild TBI

S10-03

ABBREVIATED ENVIRONMENTAL ENRICHMENT CONFERS ROBUST NEUROBEHAVIORAL AND COGNITIVE BENEFITS IN BRAIN INJURED FEMALE RATS

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To establish an efficacious therapy for traumatic brain injury (TBI) a variety of relatively invasive strategies have been evaluated. Environmental enrichment (EE) is a non-invasive paradigm that promotes significant cognitive recovery after experimental TBI and has the potential to mimic post-TBI neurorehabilitation. However, the typical EE paradigm consists of continuous exposure, which is inconsistent with the clinic where physiotherapy is typically limited (Matter et al., 2011). Moreover, females make up approximately 40% of the clinical TBI population, yet they are rarely studied in TBI research. Hence, the goal of this study was to *test the hypothesis that abbreviated EE would confer neurobehavioral and cognitive benefits in brain injured female rats*. Anesthetized female rats received a controlled cortical impact (2.8 mm tissue deformation at 4 m/s) or sham injury (i.e., no impact) and were randomly assigned to TBI + EE (4 hr), TBI + EE (6 hr), TBI + EE (continuous), or TBI + STD groups, and respective sham controls. Motor function (beam-balance/beam-walk and rotarod) was assessed on post-operative days 1–5 and every other day from 1–19, respectively. Spatial learning/memory (Morris water maze) was evaluated on days 14–19. The data showed that EE, regardless of dose, improved motor function compared to STD housing ($p < 0.0001$). However, only continuous and 6-hr EE enhanced cognitive function ($p < 0.0001$). These data demonstrate that abbreviated EE confers robust neurobehavioral and cognitive benefits in TBI female rats, which supports the hypothesis and strengthens the validity of EE as a pre-clinical model of neurorehabilitation. Ongoing studies from our laboratory are evaluating further the benefits of abbreviated EE by combining it with pharmacotherapies, which may result in additive or synergistic benefits, thus facilitating recovery after TBI.

Keywords: Brain Injury, Controlled Cortical Impact (CCI), Environmental Enrichment, Females

S10-04

NEUROINFLAMMATORY MYELOID CELL PROCESSES ASSOCIATE WITH DIFFUSELY INJURED AXONS FOLLOWING MILD TRAUMATIC BRAIN INJURY IN MICROPIGS

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Mild traumatic brain injury (MTBI) is a prevalent disease that exacts significant personal and societal cost. The pathophysiology of MTBI is complex, with reports of diffuse axonal injury (DAI) being highly correlated to prolonged morbidity. Progressive chronic neuroinflammation has also recently been correlated to morbidity, however, the potential association between neuroinflammatory myeloid cells and DAI is not well understood. The majority of studies exploring neuroinflammatory responses to TBI have focused on more chronic phases of injury and phagocytosis associated with Wallerian change. Little, however, is known regarding the neuroinflammatory responses seen acutely following diffuse MTBI and potential relationships to early DAI, an issue that has significant clinical relevance. Additionally, inflammation has recently been shown to be drastically different in rodents as compared to gyrencephalic humans. Accordingly, we employed a modified central fluid percussion model of MTBI in gyrencephalic micropigs and assessed potential associations between acute DAI and neuroinflammation within 6h of injury. This model generated substantial DAI in the thalamus (10.31 ± 1.34 APP+ swellings/0.72 mm^2 field), an area commonly affected across the spectrum of TBI. Extensive neuroinflammation was also observed following MTBI in the same thalamic sectors. Importantly, physical contact between Iba-1+ myeloid cell processes and the APP+ swellings of axons sustaining DAI was nearly double (0.16 ± 0.02 contacts/mm) compared to uninjured myelinated axons in sham animals (0.09 ± 0.01 contacts/mm). While active phagocytosis was observed in association with Wallerian degeneration, the Iba-1+ cells that contacted DAI swellings did not reveal

ultrastructural changes consistent with phagocytosis. This is the first study to show direct physical correlation between the acute phase proximal axonal swellings and non-phagocytic neuroinflammation in a higher order animal. These findings could lead to a more complete understanding of acute neuroinflammation following MTBI and its potential as a diagnostic and/or a therapeutic target. This work was performed as a component of the Operation Brain Trauma Therapy consortium, which is supported by DoD grant W81XWH-10-1-0623.

Keywords: Neuroinflammation, Diffuse axonal injury, Micropig, Central fluid percussion injury, Quantitative image analysis

S10-05

CHARACTERIZATION OF ENDOGENOUS BRAIN-DERIVED NEUROTROPHIC FACTOR EXPRESSION IN RESPONSE TO PENETRATING BALLISTIC-LIKE INJURY

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Brain-derived neurotrophic factor (BDNF) has been shown to play a key role in mediating neurogenesis and synaptic plasticity in the adult central nervous system. However, little is known about the changes in this endogenous molecule following penetrating ballistic-like injury (PBBI). The aim of this study was to identify the regional and temporal alterations in BDNF levels in relationship to downstream neuroplasticity markers in the PBBI model. Adult male Sprague-Dawley rats received either sham (craniotomy only) or PBBI (10% injury severity) surgery, and were euthanized at 24h, 48h, 72h, and 7 days post-injury for BDNF quantification, and at 7, 14 and 28d post-injury for neuroplasticity assessments ($n = 5–6$/time-point). BDNF levels were quantified in hippocampus and cerebral cortex by ELISA assay, and growth-associated protein-43 (GAP-43) and synaptophysin (SYN) immunohistochemistry was performed to assess axonal and synaptic plasticity, respectively. Following immunostaining, the integrated density in the hippocampal region was determined using NIH Image J software. Results showed significant reductions in BDNF levels that were detected bilaterally in cortical and hippocampal regions at 7 days post-injury ($p < 0.05$ vs. sham), but not at the earlier time points. PBBI significantly decreased GAP-43 expression in the ipsilateral hippocampus at 14d and 28d post-injury, and in the contralateral hippocampus at 14d post-injury ($p < 0.05$ vs. sham). Similarly, significant reductions in SYN staining were detected at 14d and 28d post-injury in the ipsilateral hippocampus and at 14d post-injury in the contralateral hippocampus ($p < 0.05$ vs. sham). Collectively, these findings demonstrate that PBBI results in a delayed down-regulation of BDNF levels that precede subsequent reductions in neuroplasticity markers. These results suggest a critical role of BDNF in modulating endogenous neuroplastic response to brain injuries, underscoring the potential importance of supplementing growth factors to enhance neuroplasticity for promoting functional recovery after PBBI.

Keywords: BDNF, Synaptophysin, GAP-43, PBBI

S11 Open Communication: SCI

S11-01

THE CGRP8-37 RECOMBINANT PEPTIDE CONSTRUCT TO REDUCE CHRONIC PAIN FROM RAT SPINAL CORD INJURY

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Chronic pain following spinal cord injury (SCI) is challenging clinical problem with few effective treatments. It is necessary to identify new therapeutic targets and approaches. Calcitonin gene related peptide (CGRP) is produced by neurons in the dorsal root ganglia and thought to play a key role in nociceptive neurotransmission in the spinal dorsal horn. Hypersensitivity to CGRP and/or sprouting in response to injury may contribute to allodynia and hyperalgesia in persistent neuropathic pain. A truncated CGRP peptide, $CGRP_{8-37}$, can reverse symptoms of neuropathic and inflammatory pain in animal models. This study aims to test the analgesic potential of the neuropathic pain gene therapy candidate $CGRP_{8-37}$. The $CGRP_{8-37}$ fragment from human CGRP cDNA was cloned to the peptidylglycine-amidating monooxygenase (ssPAM/pGEMT) signal peptide to allow $CGRP_{8-37}$ to be amidated and secreted, and subcloned into AAV- and Lenti-EGFP plasmids. Immunocytochemical colocalization of anti-CGRP and Golgi marker anti-Giantin antibody confirmed secretable $CGRP_{8-37}$ peptide. For initial screening, $CGRP_{8-37}$ supernatant transfected HEK cells was intrathecally injected into rats with chronic constriction injury (CCI) and formalin-evoked inflammatory pain model. Results showed that reduction of mechanical, tactile, cold allodynia and formalin-evoked pain responses treated with AAV-$CGRP_{8-37}$ supernatant was comparable with the effect of 10 nM $CGRP_{8-37}$ peptide, but not in controls. Spinal cord clip compression injury was induced pain-related behavior in rats. At 4 weeks post-injury when pain-related behavior was clearly established, animals were injected with lenti-ssPAM-$CGRP_{8-37}$-EGFP or control virus intraspinally into lumbar dorsal horn. Attenuation of tactile, mechanical and cold allodynia was observed by 2 weeks post injection with gradual improvement of behavioral outcomes towards pre-injury levels by 12 weeks post-SCI. In contrast, allodynia persisted in rats receiving control virus. Our findings suggest that engineered analgesic $CGRP_{8-37}$peptide have the potential to alleviate SCI-induced pain.

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Keywords: CGRP8-37, spinal cord injury, gene therapy, chronic pain

S11-02

LONGITUDINAL OPTOGENETIC MAPPING OF THE CORTICOSPINAL TRACT AS A NOVEL APPROACH FOR FUNCTIONAL EVALUATION OF SPINAL CORD INJURY

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Spinal cord injury (SCI) causes immediate disruption of ascending and descending pathways, which are commonly followed by plasticity and reorganization of these pathways at various levels of the central nervous system. For the motor system, evaluating longitudinal changes in the integrity and function of the corticospinal tract (CST) following SCI is important for understanding injury mechanisms and assessing the efficacy of therapeutic interventions. However, no techniques are currently available for this purpose. Our goal was to use *in vivo* transcranial optogenetic mapping of the motor cortex for longitudinally assessing the

function of the CST after SCI. In transgenic mice that expressed channelrhodopsin-2 in cortical layer V pyramidal neurons, we used a blue laser to scan the region of motor cortex through intact skull. Optogenetically evoked limb movements were precisely detected by motion detectors or by recording electromyogram (EMG). In uninjured mice, motor maps of the forelimb area made at different times were generally stable and reproducible. To determine whether optogenetic mapping would reflect CST function at different stages after SCI, we simultaneously assessed changes in motor maps and motor behavior of the forelimb before and at different times following unilateral pyramidotomy or cervical spinal hemicontusion. Unilateral pyramidotomy caused immediate loss of the forelimb motor area, which was followed by partial recovery of motor map and behavior in 3–4 weeks after SCI. In contrast, spinal hemicontusion at the cervical level (C5) resulted in an acute expansion of the motor map, which was followed by progressive loss of map area and impairment of motor behavior at 3–4 weeks after injury. Further analyses indicated positive correlations between map size and motor function. We conclude that optogenetic mapping of cortical motor area may be an efficient and minimally invasive technique for longitudinal functional evaluation of the CST following SCI.

Keywords: Optogenetic, Motor cortex, Spinal cord injury, Corticospinal tract

S11-03

3D IMAGING OF AXONS IN TRANSPARENT SPINAL CORDS FROM RODENTS AND NON-HUMAN PRIMATES

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Failure of axons to regenerate is the primary reason for paralysis after spinal cord injury (SCI). Thus, discovering mechanisms to promote axon regeneration has been an intense area of research. A technical challenge has been visualizing axon trajectory in the injured spinal cord to provide clear origin-target information. Recent advances in tissue clearing methods have made it possible to overcome this hurdle, but previous studies have been performed with transgenic mice in which the axons were pre-labeled with green fluorescent protein (GFP). Thus, while these studies have provided a proof-of-concept, a more practical approach to investigating axon regeneration requires axon tracing. Using mouse and rat models of SCI, we labeled different axon tracts using several types of adeno-associated viruses and performed tissue clearing to image axons using light sheet (LSFM) and confocal microscopy. AAV8-pUBC-eGFP and tdTomato viral axon labeling combined with a tetrahydrofuran (THF)/benzyl alcohol-benzyl benzoate (BABB) tissue clearing method is effective in visualizing different axons in the intact and injured mouse and rat spinal cord. While a LSFM can image the spinal cord with exceptional speed, fine axonal projections such as corticospinal axons are better suited for confocal microscopy imaging.

Keywords: Clearing, LSFM, Spinal cord injury, Light sheet fluorescence microscopy, 3Disco, CST and RST

S11-04

TARGETING THE TRPV4 CHANNEL TO REDUCE INFLAMMATION AND IMPROVE OUTCOME FOLLOWING SCI

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Trauma to the spinal cord elicits a profound inflammatory response both within the damaged cord as well as throughout the rest of the body. This inflammatory response is further characterized by the activation and mobilization of systemic as well as CNS immune components that are thought to provide both beneficial as well as pathological aspects to the healing process. Mechanisms underlying the activation and progression of this immune/inflammatory activation continue to be unveiled. The Transient Receptor Potential channel, subfamily V, member 4 (TRPV4) is a calcium-permeable, non-selective cation channel expressed throughout the body and serves as a molecular and mechanical sensor to detect alterations in temperature, osmolality blood pressure, etc. Due to TRPV4's association with endothelial cells and role as regulator of vascular tone, we hypothesized that aberrant activation of TRPV4 via mechanical insult may worsen spinal vascular leakage produced by contusion injury. We determined that blood-spinal cord-barrier (BSCB) breakdown was reduced in TRPV4-null mice compared to wild type (WT) when assessed 48 hours post-spinal contusion injury. Utilizing additional mutant mice in which TRPV4 is linked to GFP, we observed strong co-association of GFP with both spinal microglia as well as splenic macrophages. This lead us to hypothesize that TRPV4 activation following spinal cord injury (SCI) may contribute to systemic immune activation/inflammation following SCI. WT mice were treated with the selective TRPV4 inhibitor, HC-067047, once daily (10 mg/kg) for three days. We observed that HC-067047 treatment lead to a significant reduction in both microglial and astrocytic activation at the lesion site compared to vehicle-treated controls. In addition, HC-067047-treatment significantly attenuated the loss in splenic mass normally observed following CNS trauma. Our results suggest that trpV4 inhibition may attenuate both spinal and systemic immune activation/inflammation following SCI.

Support provided by: 1) Mission Connect, a Project of the TIRR Foundation, and 2) The Gillson-Longenbaugh Foundation.

Keywords: blood spinal cord barrier, spleen, neuroimmune, trpv4, macrophages

S11-05

ATTENUATING GASTROINTESTINAL VASCULAR PERMEABILITY AFTER SPINAL CORD INJURY

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Gastrointestinal (GI) hemorrhage is a dangerous complication after spinal cord injury (SCI). Undiagnosed abdominal complications are the third leading cause of death in paraplegic and quadriplegic patients after the acute phase of injury. The main objectives of this study is to investigate the compromise of the GI vascular permeability in mice during the acute phase of injury and to determine if this compromise can be attenuated by an intravenous (IV) administration of angiopoietin-1 (Ang-1). Ang-1 is a vascular stabilizing protein expressed constitutively by endothelial cells, pericytes, astrocytes, smooth muscle cells, and fibroblasts. The study examined GI vasculature permeability using dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) 48 hours after a spinal contusion injury. The contusion injury was delivered using the Infinite Horizon Impactor (60 kDynes with a 1 second dwell time) at thoracic level 8. Treatments groups received a single IV administration of Ang-1 (30 μg, 100 μg, or 300 μg) through the jugular vein three hours

following injury. Controls groups received an IV administration of saline. DCE-MRI analysis indicated that there is a significant increase in GI vascular permeability in injured animals compared to uninjured animals at 48 hours after injury. We observed a significant decrease in GI vascular permeability following a single IV injection of Ang-1 (300 μg) compared to saline treated animals. In addition, Ang-1 treatment produced a qualitative improvement in GI morphological outcome. SCI produced disruption in GI villi compared to naive, uninjured control mice in H&E stained GI tract sections. Ang-1 (300 μg) treated animals exhibited reduced GI villi damage compared to vehicle-treated subjects. Taken together the data suggests that promoting vascular stability following SCI by an IV administration of Ang-1 not only reduces GI vascular permeability but also appears to preserve intestinal villi.

Keywords: gastrointestinal, dynamic contrast enhanced imaging, vascular permeability

S12 Open Communication: Clinical

S12-01

A PROGNOSTIC MODEL FOR DETERMINING ONE-MONTH OUTCOMES IN MILD TRAUMATIC BRAIN INJURY

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There are currently no tools for aiding emergency physicians in educating mild traumatic brain injury (mTBI) patients regarding the prognosis of their injury. We sought to derive a model for identifying mTBI patients at risk for incomplete recovery from their symptoms at 1-month after injury. We analyzed data from a prospective cohort of TBI patients presenting to an urban emergency department (ED) (The ***Head*** injury ***S***erum ***M***arkers for ***A***ssessing ***R***esponse to ***T***rauma [HeadSMART] cohort). Subjects presenting within 24 hours of injury were interviewed on the day of injury. Telephone interviews were performed at 1-month after injury to determine TBI outcomes. Incomplete recovery was defined as Glasgow Outcome Scale Extended (GOSE) < 8. Prognostic models were built using univariable and multivariable logistic regression methods and stepwise selection procedures. A total of 194 subjects were enrolled between April 2014 and February 2015. Of this number, 108 were mTBI patients with a presenting Glasgow Coma Scale (GCS) of 14 or 15; a negative head CT scan; and 1-month follow-up data were included in this analysis. Within this subpopulation, 52.8% (57/108) had GOSE < 8 at 1 month. Predictor variables included in the final prognostic model were altered mental status at presentation (AMS), gender, race (African-American or non-African American), work-related injury, dangerous injury mechanism (ejection from motor vehicle, pedestrian struck, fall from height > 3ft or 5 stairs), and other injury (solid organ injury or bony fracture). This model discriminated between subjects with and without incomplete recovery with an area under the receiver operator curve (AUC) of 0.82 (95% CI: 0.73 – 0.88). A HeadSMART30 score was computed by assigning a score of 2 for AMS, 1 for female gender, 2 for African-American, 2 for work-related injury, 1 for dangerous mechanism and 1 for other injury. Subjects with a HeadSMART30 < 7; 7 and 8; 9 and 10; and greater than 10 had a 1-month risk of incomplete recovery of 0%, 27%, 71% and 86% respectively. This study provides preliminary evidence that prognostication of mTBI outcome using readily available clinical and demographic data is feasible.

Keywords: prognostic models, GOSE, TBI

S12-02

AN INITIAL EVALUATION OF THE NINDS PHENOTYPING COMMON DATA ELEMENTS FOR TRAUMATIC BRAIN INJURY

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Introduction: In 2010, the NIH and other federal agencies identified a list of Common Data Elements (CDE) that might be used in traumatic brain injury (TBI) research. The selection of these instruments was not empirically based, but was guided by their availability in the public domain, the availability of alternate forms, and, most importantly, expert opinion regarding the utility of the tests. The present study undertakes an empirical examination of these instruments, comparing their performance to other tests.

Methods: A total of 111 (62% male) subjects who had sustained a closed head injury were seen at 30, 90, 180 and/or 365 days post injury. Subjects were administered eight of the ten original ''core'' neuropsychological CDE's, two ''core'' CDE's were replaced by equivalent ''supplemental'' measures. Subjects were also administered seven additional ''supplemental'' CDE's, as well as additional well validated, commonly used neuropsychological tests. The percentage of individuals classified as ''impaired'' (scoring less than one standard deviation below the mean) was calculated for each time point and by severity.

Results: Our cohort included 60 mild, 33 moderate, and 18 severe patients with TBI. Of the original CDE's, the Trail Making Tests (TMT) A and B and California Verbal Learning Test (CVLT-2) were the most sensitive, identifying impairment regardless of patient severity or time since injury. Other original CDE tests, such the Wisconsin Card Sort did not perform as well. In addition, some other tests, such as the Booklet Category Test, Sea Shore Rhythm Test, Controlled Oral Word Association Test, Grooved Pegboard, and Finger Tapping Tests consistently identified impairment, outperformed the original CDE's.

Conclusions: Only some of the current CDE's were useful in our cohort. These included: TMT A and B, BSI and CVLT-2. In addition, a number of tests not included as original CDE's demonstrated sensitivity in the evaluation of TBI subjects and are recommended for use in this population.

Keywords: Common Data Elements, Neuropsychological, Outcomes, Phenotyping

S12-03

ADOLESCENT TRAUMATIC BRAIN INJURY INCREASES ALCOHOL CONSUMPTION AND REWARD IN FEMALE MICE

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Traumatic brain injury (TBI) is inextricably and bidirectionally linked with alcohol use. Some estimates implicate alcohol intoxication in one-third to one-half of all TBI cases. Alcohol use following injury can

reduce the efficacy of rehabilitation and greatly increase the chances for additional injury. Additionally, there is mounting evidence that TBI itself may be a risk factor for the development of alcohol use disorders. Finally, patients injured in childhood have poorer overall life outcomes and a much greater likelihood of developing substance abuse disorders. We used a standardized closed head injury to model mild traumatic brain injuries. We found that mice injured during adolescence but not during adulthood exhibited much greater alcohol self-administration in adulthood. Further, this phenomenon was limited to female mice as there was no effect of injury in males. Using behavioral testing, we determined that increased drinking behavior is mediated by alterations in the rewarding properties of alcohol and not sensory deficits from TBI. Environmental enrichment administered after injury reduced axonal degeneration and prevented the increase in drinking behavior. Additionally, brain derived neurotrophic factor gene expression, which was reduced by TBI, was normalized by environmental enrichment. Finally, an analysis of human data indicated that girls injured during early adolescence were much more likely to misuse alcohol as adults than were girls injured during other developmental epochs. Together these results suggest a novel model of alterations in reward circuitry following trauma during development.

Keywords: Alcohol, Adolescent Injury, Environmental Enrichment, BDNF, Inflammation, Concussion

S12-04

SINGLE EPISODE OF SEVERE AXONAL INJURY IN HUMANS IS ASSOCIATED WITH PATHOLOGY RESEMBLING CHRONIC TRAUMATIC ENCEPHALOPATHY

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Chronic traumatic encephalopathy (CTE) is a neurodegenerative disorder associated with repetitive mild traumatic brain injury (TBI). In CTE, abnormal *tau* proteins aggregate in a distinctive pattern of neurofibrillary tangles (NFTs) and astrocytic tangles favoring sulcal depths, perivascular regions and superficial neocortical layers. It has been suggested that these *tau* aggregates develop following axonal damage and/or impact-related mechanical stresses.

We analyzed postmortem brains from six schizophrenic patients who had undergone prefrontal leucotomy prior to 1953 and then lived at least another 40 years. Because leucotomy involves severing axons of the prefrontal cortex, this procedure represents a single TBI with severe axonal injury and no external cortical impact. We examined cortical tissues at the leucotomy sites, prefrontal and caudal frontal cortices and hippocampi. We compared these specimens to brains of six age-matched, non-leucotomized schizophrenics. We conducted immunohistochemistry using antibodies against abnormal *tau,* β-amyloid and astrocytes. We performed APOE genotyping for the six leucotomy patients.

In all six leucotomy cases, prefrontal lesion sites revealed severe white matter damage. Abnormal *tau* (NFTs and astrocytic tangles) was detected in cortex adjacent to leucotomy sites, involving depths of sulci, perivascular regions and superficial neocortical layers, but not in prefrontal and caudal frontal cortices distant to the leucotomy lesions. Similarly, β-amyloid plaques occupied the gray matter adjacent to the lesion sites, but only in the three patients with APOEε4 haplotypes. Non-leucotomized schizophrenic patients showed no significant pathology.

Massive chronic axonal damage in white matter, as produced in leucotomy, leads to abnormal *tau* in neurons and astrocytes in gray matter adjacent to the lesion in the distinctive pattern resembling CTE. These data suggest that chronic neuronal deafferentation alone leads to abnormal *tau* accumulation. Because leucotomy lacks external cortical impact, the data suggest that selective accumulation of *tau* at depths of sulci may be related to underlying axonal damage rather than mechanical stresses during TBI. Lastly, only patients with the APOEε4 haplotype formed β-amyloid plaques.

Keywords: CTE, Axonal injury, tau, neuropathology

S12-05

TRAUMATIC AXONAL INJURY IN THE LIVING HUMAN BRAIN: CONCORDANCE OF MICRODIALYSIS AND ADVANCED MRI APPROACHES

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We performed microdialysis and diffusion tensor imaging in the same cohort of 15 severe traumatic brain injury patients to assess axonal injury with 2 complementary approaches. 100 kDa cut-off microdialysis catheters were implanted at a median time of 17 h (13–29 hours) after injury in normal appearing (on CT scan) frontal white matter in all patients. Diffusion tensor MRI scans at 3T were performed 2–9 weeks after injury in 11 patients. Stability of diffusion tensor imaging findings was verified by repeat scans 1–3 years later in 7 patients. An additional 4 patients were scanned only at 1–3 years after injury. Imaging abnormalities were assessed based on comparisons with 5 controls (healthy subjects) for each patient, matched by age and sex (32 controls in total).

We found that acute microdialysis measurements of the axonal cytoskeletal protein tau in the brain extracellular space correlated well with diffusion tensor MRI-based measurements of reduced brain white matter integrity in the 1 cm radius white matter-masked region near the microdialysis catheter insertion sites. Specifically, we found a significant inverse correlation between microdialysis measured levels of tau 13–36 hours after injury and anisotropy reductions in comparison with healthy controls (Spearman $r = -0.64$, $p = 0.006$). Anisotropy reductions near microdialysis catheter insertion sites were highly correlated with reductions in multiple additional white matter regions. We interpret this result to mean that both microdialysis and diffusion tensor MRI accurately reflect the same pathophysiological process: traumatic axonal injury. This cross-validation increases confidence in both methods for the clinical assessment of axonal injury. Future work will be required to determine the prognostic significance of these assessments of traumatic axonal injury when combined with other clinical and radiological measures.

Keywords: microdialysis, diffusion tensor imaging, tau

S13 Brain Injury: Effects on Physiology and Function Beyond the Brain

S13-01

HEPATIC AND SPLENIC CONTRIBUTIONS TO TRAUMATIC BRAIN INJURY

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Each year, traumatic Brain Injury (TBI) impacts millions of people worldwide. Despite the increased resources dedicated to understanding the complex series of physiological events that follow a TBI, effective diagnostic and treatment options are lacking. Following a TBI, there is a rapid, innate neuroinflammatory and inflammatory response. This response includes activation of astrocytes and microglial cells in the central nervous system (CNS), as well as expansion, activation and infiltration of peripheral immune cells into the CNS. Our recent data, as well as data from a few select other groups, have demonstrated that following a TBI, there is evidence for a transition from an innate to an adaptive immune response. This response appears to involve both the liver and the spleen. This evidence for an adaptive immune response to a TBI will be presented, as will our data highlighting the innate immune response to TBI. In addition, data will be shown to illustrate that targeting the transition from an innate to an adaptive immune response provides neuroprotection following a TBI. The broad impact of such findings will be further contextualized to allow for a discussion of the potential impact on the short- and long-term consequences of targeting the switch to an adaptive immune response for the treatment of TBI.

Keywords: Peripheral immune system, Liver, Spleen, CD74, MHC, Invariant Chain

S13-02

NEUROGENIC IMMUNE DEFICIENCY AFTER SPINAL CORD INJURY: MECHANISMS OF ACTION AND THERAPEUTIC OPPORTUNITIES

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Most who suffer a traumatic spinal cord injury (SCI) above spinal level T5 develop autonomic dysreflexia (AD), a pathological condition characterized by severe episodic paroxysmal hypertension. Untreated, AD can cause pulmonary embolism, stroke or even death. Data from our lab indicate that maladaptive plasticity in the spinal cord circuitry responsible for causing AD also causes chronic immune suppression. In SCI mice, the onset and frequency of AD correlates with the magnitude of immune suppression. We predicted that as large segments of spinal cord lose supraspinal input, the periodic activation of viscera-sympathetic reflexes (e.g., due to bladder/bowel filling) will cause uncontrolled activation of sympathetic motor neurons with heightened release of catecholamines and glucocorticoids (GCs) into blood and lymphoid tissues. Data indicate that GC and catecholamine-dependent signaling synergizes to elicit apoptosis in leukocytes and that remaining immune cells are functionally impaired. Retrograde trans-synaptic labeling from the spleen of SCI mice reveals the formation of new and complex intraspinal circuitry, presumably due to ongoing plasticity and synaptogenesis between primary sensory afferents, interneurons and sympathetic preganglionic neurons. Moreover, the receptive field for activating this new circuitry expands beyond the thoracic spinal segment that controls secondary lymphoid tissues in naïve/uninjured mice. Thus, after SCI, an uncontrolled ''supercharged'' autonomic circuit develops that recapitulates convulsive neuropathology (''autonomic spinal epilepsy'') and causes immune suppression. New preliminary data indicate that this aberrant circuitry can be ''silenced'' and immune cell ablation reversed by injecting inhibitory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) into the spinal cord. Neurogenic immune ablation may explain why people with high-level SCI are more susceptible to infection – a leading cause of morbidity and mortality in this patient population. Overcoming this deficit will reduce mortality, significantly improve quality of life and also recovery of neurological function after SCI. Supported in part by NIH-NINDS R01NS083942 (PGP), Dept. of Defense (W81XWH-13-1-0356).

Keywords: Autonomic Dysreflexia, hypertension, maladaptive plasticity, Spinal Cord Injury, immune Suppression

S13-03

INTESTINAL BARRIER DYSFUNCTION AFTER TRAUMATIC BRAIN INJURY

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The physio-logic connection be-tween the brain and the gut has recently been coined the ''neuro-enteric axis.'' In this regard, in-ves-tigators have established the unique in-ter-play and com-mu-nication be-tween parts of the brain, namely the dorsal motor nucleus of the vagus nerve, the vagus nerve and the in-testine itself. Our laboratory has demon-strated that severe TBI causes sig-nifi-cant in-testinal dysfunc-tion. Inter-estingly, by electrically stimulating the vagus nerve, we have shown post-TBI intestinal injury to be sig-nifi-cantly mitigated. When the para-digm was reversed, vagus nerve stimulation actually impro-ved blood brain barrier leakage and neu-ronal degene-ration fol-lowing severe TBI. How vagus nerve stimulation may affect the neuro-enteric axis in unknown. It is likely not purely secondary to the known anti-in-flam-matory effects of the vagus nerve. These modulators and signals may very well be from gut derived neuro-endo-crine hormones.

Keywords: intestinal barrier dysfunction, neuroendocrine hormone, vagus nerve

S14 Purines - Forgotten Mediators in CNS Injury

S14-01

ROLE OF THE 2′,3′-CAMP-ADENOSINE PATHWAY IN TRAUMATIC BRAIN INJURY

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Using mass spectrometry, we recently discovered that some tissues generate a positional isomer of 3′,5′-cAMP, namely 2′,3′-cAMP. Additionally, we established that: 1) the biosynthesis of 2′,3′-cAMP is stimulated by cellular injury; 2) 2′,3′-cAMP derives from the breakdown of mRNA; 3) 2′,3′-cAMP is exported to the extracellular compartment; and 4) extracellular 2′,3′-cAMP is metabolized to 2′-AMP and 3′-AMP, which are subsequently metabolized to extracellular adenosine. We call this biochemical sequence (intracellular 2′,3′-cAMP⇒extracellular 2′,3′-cAMP⇒2′-AMP/3′-AMP⇒adenosine) the ''2′,3′-cAMP-adenosine pathway.'' Emerging evidence suggests that intracellular 2′,3′-cAMP promotes opening of brain mitochondrial permeability transition pores and that extracellular adenosine is a key neuroprotective autacoid. Thus we hypothesize that the 2′,3′-cAMP-adenosine pathway may be an important mechanism for protection against neurotrauma. In support of this concept, we find that neurons, oligodendrocytes, astrocytes, and microglia convert 2′,3′-cAMP mostly to 2′-AMP (with oligodendrocytes being most efficient) and 2′-AMP to adenosine (with microglia being most efficient), and knockout of 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNPase) attenuates the ability of oligodendrocytes to metabolize 2′,3′-cAMP to 2′-AMP. Microdialysis experiments in mice demonstrate that traumatic brain injury (TBI; controlled cortical impact) activates the

brain 2′,3′-cAMP-adenosine pathway; similar experiments in CNPase knockout mice suggest that CNPase is involved in the metabolism of endogenous 2′,3′-cAMP to 2′-AMP and to adenosine and provides neuroprotection. In CSF from TBI patients, 2′,3′-cAMP is increased in the initial 12 hours after injury and correlates with CSF levels of 2′-AMP and adenosine. We conclude that the 2′,3′-cAMP-adenosine pathway exists in the brain and is likely neuroprotective.

Keywords: 2', 3'-cAMP, 2'-AMP, 3'-AMP, Adenosine, CNPase

S14-02

ROLE OF ADENOSINE IN POSTTRAUMATIC SEIZURES AND EPILEPSY: A POTENTIAL NEW TARGET

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Brain trauma and related injuries trigger a sequela of events that cause glial activation. Astrogliosis is a major consequence of traumatic brain injury and associated with increased expression of the major adenosine metabolizing enzyme adenosine kinase (ADK); those changes result in adenosine deficiency as characteristic chronic response of affected brain areas to a prior injury. In rodent models of neuronal injury and epilepsy we have demonstrated that *(i)* overexpression of ADK and resulting adenosine deficiency can be a direct cause for epileptic seizures, and *(ii)* that adenosine deficiency induces changes to the epigenome resulting in increased DNA methylation status. Based on those mechanisms, adenosine augmentation therapies hold promise for the treatment, as well as prevention, of posttraumatic epilepsy. Data are presented showing that therapies that reconstruct adenosine homeostasis locally (e.g. by adenosine releasing bioengineered brain implants, or gene therapy) can effectively suppress epileptic seizures in rodent models of epilepsy. Furthermore, transient therapeutic adenosine augmentation affects pathogenic changes of the epigenome (i.e., hypermethylation of DNA) long-term and thereby prevents the development and progression of epilepsy.

Keywords: adenosine, adenosine kinase, silk, epigenetics, DNA methylation, epileptogenesis

S14-03

URATE - A NOVEL POTENTIAL THERAPY IN CNS INJURY AND NEURODEGENERATION

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Urate elevation has recently emerged as a promising and realistic neuroprotective strategy for the treatment neurodegenerative diseases and acute neuronal injury. Urate (a.k.a. uric acid) circulates at higher levels in humans and other hominoids due to mutations in the gene encoding the urate-catabolizing enzyme urate oxidase (UOx) during primate evolution. Although the increased levels now predispose humans to urate crystal disorders like gout, they likely conferred an evolutionary advantage to our ancestors. The discovery that urate has potent antioxidant properties equivalent to those of ascorbate and is the main source of antioxidant capacity in human plasma led to the theory that urate serves as an endogenous protectant against diseases characterized by oxidative damage, including Parkinson's disease (PD). Higher urate has been identified as a robust inverse risk factor for PD and as a favorable prognostic biomarker among people already diagnosed with PD. Similarly, lower urate levels have been linked to the development or more rapid progression of other neurodegenerative diseases including ALS. Laboratory studies in cellular and animal models of PD have further substantiated the neuroprotective potential of urate, and interestingly have implicated an astrocyte-dependent mechanism through the Nrf2 antioxidant response pathway. Of note, the urate precursor inosine has been found to be improve recovery in animal models of spinal cord and traumatic brain injury (TBI), and both inosine and urate are markedly increased locally after TBI. Based on convergent lines of evidence suggesting that urate may be a mediator as well as a marker for slower disease progression, a randomized double-blind placebo-controlled phase 2 clinical trial of the inosine in early PD was conducted, finding that urate levels in blood and CSF could be effectively, safely and chronically elevated in this population. In parallel, urate itself has been shown to confer protection against acute cerebral ischemia in rodent models of stroke and led to a phase 2 randomized double-blind placebo-controlled phase 2 clinical trial of intravenous urate in the setting of an acute ischemic stroke, with encouraging safety and efficacy results.

Keywords: Urate, Inosine, Nrf-2, Parkinson's disease, TBI, stroke

S15 Post-Traumatic Epilepsy: Mechanisms and Manifestations

S15-01

CLINICAL RESEARCH INSIGHTS INTO PERSONAL BIOLOGY AND BIOSUSCEPTIBILTIY WITH EPILEPTOGENESIS AND POST-TRAUMATIC EPILEPSY

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Epileptogenesis and the development of Post-traumatic Epilepsy (PTE) is relatively common after moderate to severe traumatic brain injury (TBI). Clinical predictors are limited in their ability to identify those at highest risk for PTE development and to identify who may benefit most from prophylactic treatment strategies. We will review the latest evidence for clinical predictors of PTE risk, summarize points of overlapping pathophysiology with TBI and epilepsy, and explore the current evidence for genetic and proteomic biomarkers with informing the process of epileptogenesis and epilepsy development for those with TBI. Contemporary work from our laboratory will be reviewed that identifies biomarkers within inflammatory pathways as well as excitatory and neuroinbitory pathways as possible contributors to epileptogenesis and PTE. Future directions for advancing this work, including validation studies and therapeutic target exploration, will be discussed. Future opportunities for Rehabilomics based approaches to exploring biological associations with recovery based outcomes will be discussed.

Keywords: biosusceptibility, Rehabilomics, epileptogenesis, risk assessment

S15-02

SEIZURE SUSCEPTIBILITY AFTER TRAUMATIC INJURY TO THE PEDIATRIC BRAIN

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The occurrence of post-traumatic epilepsy is particularly high after injury at a young age, and has been associated with poorer functional outcomes, suggesting that the developing brain may show elevated vulnerability to post-traumatic epileptogenesis. However, most existing models of post-traumatic epileptogenesis focus on injury to the adult brain. Here, we have investigated seizure susceptibility in mice after injury at postnatal day 21, using a well-characterized model of controlled cortical impact to approximate a toddler-aged child. Within weeks, brain-injured mice

showed a pronounced seizure response to the convulsant pentylenetetrazol (PTZ) compared to sham-operated controls, coincidental with significant loss of hippocampal interneurons and pronounced astrogliosis. A heightened seizure response to PTZ was still apparent several months later at adulthood, and associated with the presence of abnormal mossy fiber sprouting in the ipsilateral hippocampus, a pathological hallmark of epileptogenesis. In addition to pleiotropic roles in neurodegeneration, several inflammatory mediators including interleukin (IL)-1β have been implicated in the initiation and propagation of seizures. Ongoing studies aim to elucidate the importance of such factors in persistent hyperexcitability in the immature brain after traumatic injury.

Keywords: interleukin-1, cytokine, immature brain, epileptogenesis

S15-03

NON-CONVULSIVE SEIZURES OBSERVED 1 YEAR FOLLOWING TRAUMATIC BRAIN INJURY

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Epilepsy is an important secondary consequence of traumatic brain injury (TBI), recognized in TBI patients and reproduced reliably in animal models of TBI. Early studies focused on convulsive seizures but non-convulsive seizures also occur after TBI that are not easily detected by behavioral analysis. In this study we examined electrocorticographic (ECoG) seizures in freely behaving rats 1 year after fluid percussion brain injury. Epidural electrodes were implanted over the ipsilateral cortex anterior and posterior to the contusion site of rats that were naïve or received sham, mild, moderate or severe TBI. 24 hrs later ECoG activity and video analysis was conducted in freely moving animals for 60 min. No animals showed convulsive seizures during the 60 min recording period. However, spontaneous spike and wave episodes were detected, which were more prevalent in animals that had undergone TBI 1 year earlier than in either naïve or sham-operated animals. The spike and wave episodes were quantified using custom seizure detection software that incorporated fast Fourier transform and normalized multi-frequency power spectral analysis. The non-convulsive seizures were accompanied by behavioral immobility or ''freezing'', which was quantified using Ethovision movement analysis software. The non-convulsive electrographic seizures and freezing behavior appeared similar to seizures described by other investigators as ''absence-like seizures'' in rodents. Our data suggest that post-traumatic epilepsy may present 1 year after TBI in rodents and may take the form of non-convulsive or sub-clinical seizures.

Keywords: chronic seizures, sub-convulsive seizures

WLW1 WINTR Lunch Workshop

WLW1-01

EXPERIENCE IN EXAMINATION OF HUMAN TBI TISSUE: A NEGLECTED ART

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Repro-ducing neuro-patho-logical features of traumatic brain injury (TBI) and its outcomes, including chronic traumatic encephalo-pathy (CTE), in animal models is a major focus of neuro-trauma research. How-ever, very few researchers have experience assessing human tissue, as neuro-patho-logical examination of human TBI brains is not a standard part of graduate training, and access to human brain tissue is limited. In ad-di-tion, post-graduate trained neuro-patho-logists with research in-ter-est or experience in TBI are few and far be-tween. As a consequence, there is a danger that appre-ciation of the range and ex-tent of patho-logies encountered in human TBI and the so called 'normal' variation in human neuro-patho-logy, for example arising through age and influence of comorbid patho-logy, is lost. Further, through lack of exposure to the variation and vagaries of working with human tissue, awareness of common artefacts and pitfalls in in-ter-pre-tation of histo-logical material can be diluted. In short, neuro-patho-logy in-ter-pre-tation of human TBI tissue is challenging and fraught with com-plexity and frustration, but if pro-gress is to be made, it is unavoidable. Whilst tempting to focus on surrogates of patho-logy in research, such as bio-marker or imaging studies, without the neuro-patho-logy to validate these observations, their in-ter-pre-tation can remain challenging and questionable. And while animal models have undoubted attraction, unless these model some aspect of human patho-logy, their value is debtable. From early neuro-patho-logical studies carefully describing and documenting diffuse axonal injury to more recent studies detailing neuro-degene-ration after TBI, the con-tri-bution of careful neuro-patho-logical examination on suitably pre-pared human brain tissue to our under-standing of the consequences of traumatic brain injury can be traced through the major milestones in TBI research and should remain in-tegral to research studies in the future. During this WINTR Workshop the challenges and benefits in working with human tissue will be reviewed, strategies to pro-ject design using human TBI material will be outlined and the history and holdings of the unique Glasgow TBI Archive will be dis-cussed.

Keywords: neuropathology, human studies, TBI, CTE

WLW1-02

BI-DIRECTIONAL TRANSLATIONAL STUDIES IN TBI: EXPERIMENTAL DESIGN USING HUMAN SAMPLES

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Traumatic brain injury (TBI) is a major health issue, exacting a considerable health and economic burden on society. Furthermore, TBI is increasingly recognized as a major risk factor for the development of neurodegenerative disorders. However, despite decades of research, no effective therapeutic agent has been successfully introduced to clinical practice, with multiple failed phase 3 trials. While the reasons for these failures are complex, the inability to translate therapeutic efficacy in animal models to clinical efficacy in humans has been a major and recurring issue and raises questions over the relevance of preclinical data. Paramount to any model is that it recapitulates pathologies arising in human TBI. Further, any novel observations in TBI generated from studies in animal models must be challenged in human tissue to confirm relevance. This bi-directional translational principle in research is central to ensuring applicability of animal models and in challenging novel observations in human tissue. As such, awareness of human neuropathology studies in TBI, in particular the strengths and limitations of this work, should be a fundamental objective for the field. Decades of careful studies examining tissue from patients following TBI reveal a heterogeneous and complex array of pathologies influenced by injury severity, comorbidities, survival time, history of previous TBI and patient age, among many other factors. As such, studies in human tissue carry complexities and challenges which must be borne in mind for study design. In particular, there is a requirement in any study for inclusion of appropriately matched controls to provide a baseline of 'normal' pathology against which pathology in TBI material can be compared. Similarly, there is a need to recognize inherent limitations in any archive of human bio-samples, such as case selection bias. Nonetheless, appropriately designed studies in

human tissue, with careful and measured interpretation, remain of utmost importance to informing relevant TBI research.

Keywords: Study Design, Translation

WLW1-03

THE GLASGOW TRAUMATIC BRAIN INJURY ARCHIVE

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As an outcome of the international, inter-disciplinary meeting on the ''Late Effects of Head Injury'' held in Washington in 1969 there was a call for the establishment of brain banks specifically dedicated to studies in traumatic brain injury (TBI). Almost a half century later, the Glasgow TBI Archive represents the only comprehensive archive of human brain tissue dedicated to studies in TBI internationally. Comprising materials from TBI patients across a spectrum of ages, the Glasgow TBI Archive represents a comprehensive and unique archive of biospecimens containing: in excess of 2000 cases of traumatic brain injury as paraffin wax blocks sampled from immersion fixed whole brain specimens; approximately 50 TBI cases as snap-frozen, fresh tissue samples; extensive, non-TBI control tissue samples as paraffin tissue blocks and snap frozen tissue; in excess of 1200 DNA samples from patients in ongoing longitudinal clinical studies in TBI. Each case has been meticulously gathered using standardised sampling protocols, with all specimens linked to demographic data, clinical information including details on injury and cause of death, post mortem interval and neuropathology findings. Under the governance arrangements of the Greater Glasgow and Clyde Health Board Bio-repository, the Glasgow TBI Archive has broad and enduring ethical approval for use in research studies via a streamlined online application to the GGC Bio-repository Steering Committee. The influence of this archive can be traced through the literature on the neuropathology of human TBI, with over 150 peer-reviewed publications derived from observation on material from this resource, including landmark and continued observations on axonal injury and neurodegeneration after TBI. The requirement for robust and informative TBI research utilising human tissue samples is as relevant now as it was in 1969. Further, there exists a pressing need to expand current archive holdings and to establish new tissue holdings to support relevant studies in the wider TBI research community.

Keywords: neuropathology, TBI archive

WNR1 WINTR Reception

WNR1

CAREER DEVELOPMENT IN NEUROTRAUMA RESEARCH

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Early career choices involve funding decisions, from pre- and post-doctoral applications at academic institutions to deciding to pursue research in the private sector, or even leave the bench or bedside to have careers in administration, law, writing or other disciplines. For those who choose academics (and the private sector) grant writing will be a big part of their endeavors. The biggest funder of biomedical research in the US is the federal government starting with NIH, followed by DoD, NSF, CDC, SAMHSA. Private foundations have always supported investigators and projects, usually targeted toward specific diseases. Navigating the funding spectrum might not be a full time job, but it is definitely a significant part of anyone's career and successful funding is critical for individuals, academic institutions and small business ventures. NIH offers various workshops, seminars, discussions, websites that can help you, but networking is critical to your success. If you are an associate, post-doc, or assistant professor, ally yourself with someone who has a grant. Get to know what they do to be successful: if it involves secret handshakes or lucky charms, don't knock it. Have them introduce you to their program officers at NIH/NSF. Go to national meetings and participate in interest groups. Publish as much as you can—find the ''least publishable unit'' for your field. If you have the opportunity, be an *ad hoc* reviewer for a funding agency. AND be good mentors to the people who will inevitably start to look to you for advice.

Keywords: NIH, career development

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