NEUROTRAUMA 2014

The 32nd Annual Symposium of the

National Neurotrauma Society

SCIENTIFIC PROGRAM

June 29 - July 2

San Francisco, CA

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Letter from the President

Dear Fellow Neurotrauma Researchers:

On behalf of the National Neurotrauma Society (NNS), I warmly welcome you to join us for The 32nd Annual Symposium of the National Neurotrauma Society, including the AANS/CNS Section on Neurotrauma and Critical Care, at the Marriott Marquis in downtown San Francisco, June 29-July 2, 2014. The theme of this year's conference is "*From Bench to Bedside and Back*".

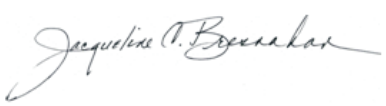
Sessions were selected by the Program Committee from many excellent topics proposed by the NNS membership, and will focus on multi-disciplinary, basic, translational, and clinical approaches to acute and chronic problems in neurotrauma. Novel topics to be addressed are the effects of repeated mild traumatic brain injuries and sports concussions, particularly for the pediatric population, autonomic nervous system challenges in both TBI and SCI, topical discussions of exciting recent data on stem cell transplantation in pre-clinical models and in clinical trials after SCI, and novel observations on the role of the lymphatic system in TBI. The Presidential Lecture will describe the ground-breaking work in human spinal cord injury utilizing spinal cord stimulation in combination with treadmill training to induce recovery of voluntary function after chronic, neurologically complete spinal cord injury. This work was chosen to highlight the important role of rehabilitation and allied health professionals in recovery from CNS injury, and the clinical application of basic science understandings to promote strategies for recovery from neurotrauma. These data will surely generate new ideas to be brought back to the lab for testing, before being brought back again for clinical evaluation. Neurotrauma survivor testimonials and an airing of "The Crash Reel", the documentary of Kevin Pearce's recovery after a snow boarding accident in preparation for the Olympics, will round out the program.

The meeting location in San Francisco provides a beautiful venue with a variety of great restaurants nearby, and we invite you to join us on a bay cruise on Tuesday evening to better view the city, the natural vistas and the remarkable bridges at sunset. Since we are meeting in June, the weather can be quite cool if you are close to the bay (think early-mid spring, especially if there is fog), but will be much warmer inland (think hot, dry summer). We hope you will enjoy being here!

No other conference combines basic science, preclinical modeling and clinical approaches to studying brain and spinal cord injury to the extent that is done in 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 San Francisco, and hope that you have an enjoyable and educational meeting!

Sincerely,



Jacqueline Bresnahan, PhD
2014 President, National Neurotrauma Society

National Neurotrauma Society

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Schedule-At-A-Glance

SUNDAY, JUNE 29

7:00 - 5:00 **REGISTRATION DESK OPEN** *Yerba Buena Grand Assembly*

7:30 - 12:00
Chinese Neurotrauma Association Meeting
Nob Hill A/B

1:00 - 2:30
WINTR Business Meeting
Nob Hill B

11:30 - 1:00
JNT Editorial Board Meeting *Nob Hill C*

2:30 - 4:00
NNS Officers & Councilors Mtg. *Nob Hill C*

8:00 - 4:00
AANS/CNS Symposium *Yerba Buena 4-5-6*

9:00 - 4:00
SFGH/UCSF 13th Annual Symposium *Yerba Buena 1-2-3*

4:00 - 4:30
Break & Visit Exhibits
Yerba Buena 7/8

4:30 - 5:15
Presidential Lecture
Yerba Buena 9

5:15 - 6:00
Public Lecture
Yerba Buena 9

6:00 - 7:30
Welcome Reception
Yerba Buena 7/8

MONDAY, JUNE 30

7:50
PRESIDENT'S WELCOME

8:00 - 10:00
Chronic Traumatic Encephalopathy & Sports Concussion
Yerba Buena 9

BREAK

10:30 - 12:00
Pediatric TBI
Yerba Buena 1-6

SCI Phase I Transplantation Clinical Trials
Yerba Buena 9

Feeding the Injured CNS
Yerba Buena 10-15

Clinical Trial Design
Nob Hill A-B-C

12:00 - 1:30
Student / Post-Doc Lunch
Club Room (2nd floor)

FREE TIME LUNCH ON YOUR OWN
All other attendees

1:30 - 3:00
Transplantation & Functional Regeneration Past a Spinal Cord Injury
Yerba Buena 9

3:00 - 4:00
Poster Session I: A1-A5 & T1-T20 Judging
Yerba Buena 7/8

Open Comm. Session I:

TBI
Yerba Buena 1-6

SCI
Yerba Buena 9

Clinical
Yerba Buena 10-15

4:00 - 5:00
Poster Session I: B1-B5
Yerba Buena 7/8

5:00 - 6:00
Wine & Cheese Open Poster Viewing
Yerba Buena 7/8

7:15 - 8:00
WiNTR Mixer & Ask an Expert
Yerba Buena 7/8 & Foyer

8:00 - 10:00
Movie Screening:
"The Crash Reel"
Followed by Q&A with Kevin Pearce
Yerba Buena 9

TUESDAY, JULY 1

7:00-7:45
NNS Business Meeting
Nob Hill A-B-C

7:50
Morning Announcements

8:00 - 10:00
Synaptogenesis after Neurotrauma
Yerba Buena 9

BREAK

10:30 - 12:00
Pediatric TBI: A Legacy of Chronic Deficit
Yerba Buena 1-6

Current Advances in Chronic TBI Cognitive Therapies
Yerba Buena 9

Innovation & Invention in Neurotrauma
Yerba Buena 10-15

12:00 - 1:30
NNS Officers & Councilors Lunch
Invitation only
Nob Hill C

FREE TIME LUNCH ON YOUR OWN
All other attendees

1:30 - 3:00
Advances in Multimodal imaging of TBI
Yerba Buena 1-6

Repeat Concussions
Yerba Buena 9

Cognitive Aging and TBI: The Role of Inflammation
Yerba Buena 10-15

3:00 - 4:00
Poster Session II: C1-C3
Yerba Buena 7/8

Open Comm. Session II:

TBI
Yerba Buena 1-6

SCI
Yerba Buena 9

Clinical
Yerba Buena 10-15

4:00 - 5:00
Poster Session II: D1-D2
Yerba Buena 7/8

5:00 - 6:00
Wine & Cheese Open Poster Viewing
Yerba Buena 7/8

7:00 - 7:30
Buses to Pier
Main Lobby

8:00 -10:00
San Francisco Bay Cruise
Buses return by 10:30 PM
Pier 43 ½

WEDNESDAY, JULY 2

7:50
Morning Announcements

8:00 - 10:00
Optimizing Rehabilitation Strategies in Neurotrauma
Yerba Buena 9

10:00 - 10:30
Awards Ceremony & iPad Drawing
Yerba Buena 9

BREAK

11:00 - 12:00
Novel Understandings and Approaches for the Future
Yerba Buena 9

12:00 - 1:30
WiNTR Lunch Workshops
Yerba Buena 1-2-3-4-5-6

FREE TIME LUNCH ON YOUR OWN
All other attendees

1:30 - 2:30
Chronic Pain and CNS Injury
Yerba Buena 9

2:30 - 4:00
Translational Concepts in Cognitive Rehabilitation
Yerba Buena 1-6

Sensory Disorders after Military Brain Injury
Yerba Buena 9

SCI & TBI Model Selection
Yerba Buena 10-15

4:00 - 4:15
Closing Remarks
Yerba Buena 9

Neurotrauma 2014
Exhibitors

General Information

Registration & Information Desk

Registration is located at the North Registration Desk near the Yerba Buena Grand Ballroom on the lower B2 level of the Marriott Marquis. Visit during these hours to reprint lost badges, ask general questions or add a ticketed event (on a space available basis).

SUNDAY, JUNE 29	7:00 AM - 5:00 PM
MONDAY, JUNE 30	7:00 AM - 5:00 PM
TUESDAY, JULY 1	7:00 AM - 5:00 PM
WEDNESDAY, JULY 2	7:00 AM - 3:00 PM

Exhibit Hours & iPad Drawing

All exhibits are located in Yerba Buena Ballroom 7/8 on the lower B2 level of the Marriott Marquis.

SUNDAY, JUNE 29	10:00am-1:00pm; 4:00pm-7:30pm
MONDAY, JUNE 30	7:00am-10:30am; 3:00pm-6:00pm
TUESDAY, JULY 1	7:00am-10:30am; 3:00pm-6:00pm
WEDNESDAY, JULY 2	7:00am-8:00am

Enter to win an iPad!
Have your Exhibitor card signed at 10 or more exhibit booths and return it to the Registration Desk to be eligible to win an iPad. The drawing will be held on Wednesday at the Awards Ceremony. Must be present to win.

Meals & Tickets

Registration for Neurotrauma 2014 includes daily continental breakfast, AM and PM coffee breaks.

Lunches are on your own, with the exception of the Student/Post Doc lunch on Monday and the WINTR Lunch workshops on Wednesday. Tickets for these lunches we sold in advance when you registered for the conference. Onsite requests to add lunch tickets cannot be guaranteed.

MONDAY
Student/Post Doc Lunch — *Lunch with the NNS Officers & Councilors. Advance RSVP required.*

WEDNESDAY
WiNTR lunch workshops — *Ticketed event ($40)*

If you have a lunch ticket and cannot attend, please let us know.

Networking & Social Events

SUNDAY
Welcome Reception — *Included for all attendees*

MONDAY
Wine & Cheese Open Poster Viewing — *Included for all attendees*
WiNTR Networking Mixer — *Included for all attendees*
Movie Screening: *"The Crash Reel"* — *Included for all attendees*

TUESDAY
Wine & Cheese Open Poster Viewing — *Included for all attendees*
San Francisco Bay Cruise — Ticketed event ($25/$50)

DAILY
Continental Breakfast/Open Poster Viewing & Coffee Breaks — *Included for all attendees*

Continuing Medical Education

This activity has been planned and implemented in accordance with the Essential Areas 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 35.25 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 27.25 CME credits for the National Neurotrauma Society sponsored portion of the entire symposium.
- The optional WINTR program is designated for a maximum of 1.5 CME credits.
- The AANS/CNS sponsored program is designated for a maximum of 6.5 CME credits.
- The SFGH/UCSF sponsored program is designated for a maximum of 5.0 CME credits, or 0.5 CEUs.

This continuing education activity meets the criteria of Virginia Commonwealth University and the Southern Association of Colleges and Schools. 3.4 CEUs will be awarded and recorded with the University (if all sessions are completed as described above).

Educational Objectives
At the conclusion of this three day symposium, attendees will be able to:
I. Describe models and new approaches to studying 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 including cellular transplantation from the laboratory to clinical trial.

CME Certificates & Evaluation Survey

To claim CME or CEU credits for the meeting, you must:

1. **Complete the survey questions for each day you attend.** You will receive an email survey at the end of each day. On the final page of the survey, you will receive a CME CODE. **You will need this code to claim your CMEs.**

2. **Login to your NNS account.** Click on the "Claim CMEs" link, then enter the CME Code and select the sessions you attended. Your CME certificate will be emailed to the address associated with your registration.

*Please note: To claim the maximum number of credits, physicians must attend the entire program. Please refer to the Continuing Medical Education section to the left for a breakdown of available credits.

Overall 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.

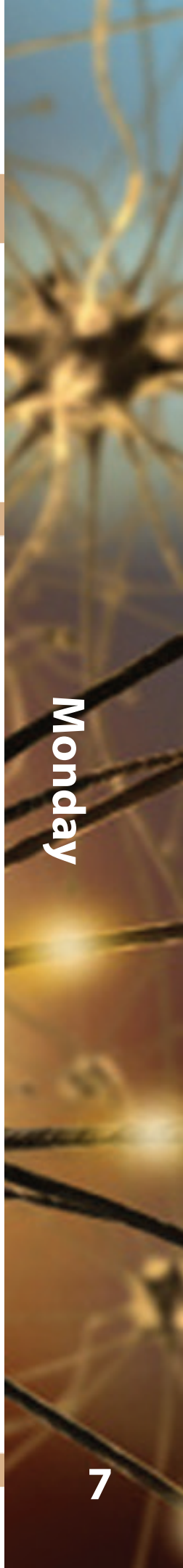
Neurotrauma 2014 Agenda
Sunday, June 29

7:00 am - 5:00 pm	Registration Open	Yerba Buena Foyer
7:00 am - 7:45 am	Continental Breakfast	Yerba Buena Foyer
7:30 am - 12:00 pm	Chinese Neurotrauma Association Meeting	Nob Hill A/B
8:00 am - 10:00 am	**AANS/CNS: Clinical Biomarkers** [2.00 CME] Chair: Uzma Samadani, MD, PhD; NYU Medical Center	Yerba Buena 4/5/6
8:00-8:40	Speech as a Biomarker for TBI - Christian Poellabauer, PhD; University of Notre Dame	
8:40-9:20	Ocular Biomarkers for TBI - Glenn Cockerham, MD; Stanford University	
9:20-10:00	Eye Tracking as a Biomarker for TBI - Uzma Samadani, MD, PhD; NYU Medical Center	
9:00 am - 12:00 pm	**SFGH/USCF 13th Annual Symposium** [2.75 CME]	Yerba Buena 1/2/3
10:00 am - 10:30 am	Coffee Break & Visit Exhibits	Yerba Buena 7/8
10:30 am - 12:00 pm	**AANS/CNS: Current Trials** [2.00 CME] Chair: Peter LeRoux, MD; Mainline Health System	Yerba Buena 4/5/6
10:30-11:00	COBRIT Trials - Ross Zafonte, DO; Massachusetts General Hospital	
11:00-11:30	Brain Oxygen Optimization in Severe Traumatic Brain Injury - Peter LeRoux, MD; Mainline Health System	
11:30-12:00	Implications & Limitations of Brain Tissue Oxygenation Clinical Trials- Ramon Diaz-Arrastia, MD, PhD; USUHS	
11:30 pm - 1:30 pm	Journal of Neurotrauma Editorial Board Meeting	Nob Hill C
12:00 pm - 1:00 pm	FREE TIME / LUNCH ON YOUR OWN	
1:00 pm - 2:30 pm	WiNTR Business Meeting - *Open to all members of WiNTR*	Nob Hill B
1:00 pm - 2:30 pm	**AANS/CNS: Controversies in SCI** [1.50 CME] Chair: Geoff Manley, MD, PhD; University of California San Francisco	Yerba Buena 9
1:00-1:30	SCI Surgery Timing: STASCIS Trial - Jefferson Wilson, MD, PhD; University of Toronto	
1:30-2:00	Use of Methyl Prednisolone in SCI: NASCIS 3 Trial - Gregory Hawryluk, MD; UCSF	
2:00-2:30	Therapeutic Hypothermia in SCI - Allan Levi, MD, PhD; University of Miami	
1:30 pm - 4:00 pm	**SFGH/USCF 13th Annual Symposium** [2.25 CME]	Yerba Buena 1/2/3
2:30 pm - 4:00 pm	NNS Officers & Councilors Meeting	Nob Hill C
2:30 pm - 4:00 pm	**AANS/CNS: Novel Therapies for SCI** [1.5 CME] Chair: Daniel Lu, MD, PhD; University of California Los Angeles	Yerba Buena 4/5/6
2:30-3:00	Brain Machine Interface - Chengyuan Wu, MD; Thomas Jefferson University	
3:00-3:30	Brain Controlled Muscle Interface - Lee E. Miller, MD; Northwestern University	
3:30-4:00	Cell Replacement Therapy for SCI - Martin Marsala, MD; University of California San Diego	
4:00 pm - 4:30 pm	Coffee Break & Visit Exhibits	Yerba Buena 7/8
4:30 pm - 5:15 pm	**Presidential Lecture: Neuromodulation & Rehabilitation After SCI** [0.75 CME] Susan Harkema, PhD; University of Louisville	Yerba Buena 9
5:15 pm - 6:00 pm	**Public Lecture: Neurotrauma Survivors: A Personal Perspective** [0.75 CME] Scott Hamilton, Circumventure Learning Corp. Roman Reed, Roman Reed Foundation Sponsored by BESINS HEALTHCARE Innovating for Well-being / BHR Pharma, LLC	Yerba Buena 9
6:00 pm - 7:30 pm	**Welcome Reception** Sponsored by Mission Connect a project of TIRR Foundation / National Neurotrauma Society	Yerba Buena 7/8

Sunday

Neurotrauma 2014 Agenda
Monday, June 30

7:00 am - 5:00 pm	Neurotrauma Registration Desk Open	Yerba Buena Foyer
7:00 am - 7:45 am	Continental Breakfast / Visit Exhibits / Open Poster Viewing [0.75 CME]	Yerba Buena 7/8
7:45 am - 8:00 am	President's Welcome - Jacqueline Bresahan PhD, UCSF	Yerba Buena 9
8:00 am - 10:00 am	**Chronic Traumatic Encephalopathy & Sports Concussions** [2.00 CME] Chair: Mayumi Prins, PhD; University of California Los Angeles	Yerba Buena 9
8:00-8:40	Chronic Traumatic Encephalopathy and Tau Bruce Miller, MD; University of California San Francisco	
8:40-9:20	Sequelae of Traumatic Brain Injury: Searching for Mechanisms and a Denominator Steven DeKosky, MD; University of Virginia Health System	
9:20-10:00	Repetitive Head Injury in Sports Mitchel Berger, MD; University of California San Francisco	
10:00 am - 10:30 am	Coffee Break & Visit Exhibits	Yerba Buena 7/8
10:30 am - 12:00 pm	**Pediatric TBI** [1.50 CME] Chair: Christpher Giza, MD; University of California Los Angeles	Yerba Buena 1-6
10:30-11:00	A Rabbit Model of Pediatric Traumatic Brain Injury Courtney Robertson, MD; Johns Hopkins School of Medicine	
11:00-11:30	Measuring Neuroplasticity and Recovery after Pediatric TBI using Advanced Neuroimaging Methods Tricia Merkley, PhD; Baylor College of Medicine	
11:30-12:00	Found in Translation: Developmental Plasticity as a Therapeutic Target after Pediatric TBI Christpher Giza, MD; University of California Los Angeles	
10:30 am - 12:00 pm	**SCI Phase I Transplantation Clinical Trials** [1.50 CME] Chair: Kim Anderson-Erisman, PhD; University of Miami	Yerba Buena 9
10:30-11:00	Phase 1 Safety Study of hESC-Derived Oligodendrocyte Progenitors (AST-OPC1) in Subjects with Neurologically Complete Thoracic SCI Edward Wirth, MD, PhD; Asterias Biotherapeutics	
11:00-11:30	Safety and Preliminary Efficacy of Purified Human Neural Stem Cells (HuCNS-SC) Transplanted 3 to 12 months Post SCI Martin Schubert, PhD; University of Zurich	
11:30-12:00	Safety and Feasibility of Autologous Human Schwann Cell (ahSC) Transplantation within 6 weeks Post SCI James Guest, MD, PhD; University of Miami	
10:30 am - 12:00 pm	**Feeding the Injured CNS** [1.50 CME] Chair: Gregory Holmes, PhD; Penn State University	Yerba Buena 10-15
10:30-11:00	Management of Nutrient Homeostasis in the Acute Phase of CNS Injury Neeraj Badjatia, MD; University of Michigan	
11:00-11:30	Update from the Bench: Where Are We in Modeling and Understanding Gastrointestinal Dysfunction? Gregory Holmes, PhD; Penn State University	
11:30-12:00	The Role of Nutrition in the Lifelong Health Status of the Neurotrauma Population David Gater, PhD; Penn State University	
10:30 am - 12:00 pm	**Clinical Trial Design - Considerations for the Future** [1.50 CME] Chair: Geoff Manley, MD, PhD; University of California San Francisco	Nob Hill A/B/C
10:30-11:00	Adaptive Clinical Trials William Barsan, PhD; University of Michigan	
11:00-11:30	Designing Inclusive SCI Clinical Trial Protocols John Steeves, PhD; University of British Columbia / ICORD	
11:30-12:00	Precision Medicine Approach for Neurotrauma Geoff Manley, MD, PhD; University of California San Francisco	
12:00 pm - 1:30 pm	FREE TIME - LUNCH ON YOUR OWN	



Neurotrauma 2014 Agenda
Monday, June 30

12:00 pm - 1:30 pm	Student / Post-Doc Lunch with NNS Officers & Councilors **Ticket required**	Club Room (Atrium level)
1:30 pm - 3:00 pm	**Transplantation & Functional Regeneration Past a SCI** [1.50 CME] Chair: Diane Snow, PhD; University of Kentucky	Yerba Buena 9
1:30-2:00	Neural Stem Cells in Models of Spinal Cord Injury Mark Tuszynski, PhD; University of California San Diego	
2:00-2:30	A Novel Growth-Promoting Pathway Promotes Propriospinal Axonal Regeneration after SCI Xiao-Ming Xu, PhD; Indiana University	
2:0-3:00	Functional Regeneration Beyond the Glial Scar Jerry Silver, MD; Case Western Reserve University	
3:00 pm - 3:45 pm	**Open Communications Session I: TBI** [0.75 CME] Chair: Theresa Currier-Thomas, PhD; University of Arizona	Yerba Buena 1-6
3:00-3:15	OC1.01 Hyperoxic versus Normoxic Resuscitation in a Rat Polytrauma Model of TBI Plus Hemorrhagic Shock Gary Fiskum, PhD; University of Maryland	
3:15-3:30	OC1.02 Global Metabolomics Profiling Reveals Metabolic Dysregulation, Oxidative Stress and Neurotransmission Alteration after Concussion Ying Deng Bryant, PhD; Walter Reed Army Institute of Research	
3:30-3:45	OC1.03 Mitochondria Associated MicroRNA Expression in Hippocampus Following TBI Joe Springer, PhD; University of Kentucky	
3:00 pm - 3:45 pm	**Open Communications Session I: SCI** [0.75 CME] Chair: David Magnuson, PhD; University of Louisville	Yerba Buena 9
3:00-3:15	OC3.01 Disrupted Autophagy After Spinal Cord Injury Is Associated with Neuronal Cell Death Shuo Liu, PhD; University of Maryland	
3:15-3:30	OC3.02 Protease Activated Receptor-Mediated Mechanisms of Neural Injury Isobel Scarisbrick, PhD; Mayo Clinic	
3:30-3:45	OC3.03 Development of a Cervical Spinal Cord Contusion Model in Non-Human Primates Ernesto Salegio, PhD; University of California San Francisco	
3:00 pm - 3:45 pm	**Open Communications Session I: Clinical** [0.75 CME] Chair: Zhifeng Kou, PhD; Wayne State University	Yerba Buena 10-15
3:00-3:15	OC5.01 Neuroendocrine-Immune Dysfunction in Individuals with Poor Outcome After Severe TBI Raj Kumar, PhD; University of Pittsburgh	
3:15-3:30	OC5.02 Phase II Clinical Trials of Cethrin in Acute Cervical Spinal Cord Injury Lisa Bond, PhD; BioAxone BioSciences	
3:30-3:45	OC5.03 Multiple Prior Concussions are Associated with Symptoms in High School Athletes Paul Berkner, PhD; Colby College	
3:00 pm - 4:00 pm	**Poster Session I: A1-A5 and T1-T20** [1.00 CME] Student Competition Final Judging	Yerba Buena 7/8
4:00 pm - 5:00 pm	**Poster Session I: B1-B5** [1.00 CME]	Yerba Buena 7/8
5:00 pm - 6:00 pm	**Wine & Cheese Open Poster Viewing** [1.00 CME]	Yerba Buena 7/8
6:00 pm - 7:15 pm	FREE TIME - ON YOUR OWN	
7:15 pm - 8:00 pm	**Networking Mixer & "Ask An Expert"** Sponsored by WiNTR	Yerba Buena 7/8 & Foyer
8:00 pm - 10:00 pm	**Movie Screening : "The Crash Reel"** Followed by Q&A with special guest speaker, Kevin Pearce Sponsored by WiNTR	Yerba Buena 9

Student Poster Competition Finalists

Judging Session: Monday, June 30 at 3:00 pm

Finalist posters are on display from Sunday - Wednesday

T-01 Grant, Daya
University of California, Los Angeles
Repeat Mild Traumatic Brain Injury in Adolescent Rats Accelerates Alzheimer's Disease Pathogenesis

T-02 Ulyanova, Alexandra
University of Pennsylvania
The Development of Epileptogenic Activity after Diffuse Brain Injury in Swine

T-03 Bressler, Scott
Boston University
Auditory Selective Attention Impairments in Blast-Exposed Veterans With Traumatic Brain Injury

T-04 Morganti, Josh
University of California, San Francisco
CCR2 Antagonism Alters Brain Macrophage Polarization and Ameliorates Cognitive Dysfunction Induced by Traumatic Brain Injury

T-05 Macolino, Christine
Thomas Jefferson University
Inflammation in the Pain Pathway in a Model of Mild Closed Head Injury: Implications for Post-Concussion Headache

T-06 Harris, James
University of Pennsylvania
Advanced Biomaterial Strategies for Micro-Tissue Engineered Neural Networks to Restore Brain Circuits

T-07 Simon, Dennis
Children's Hospital of Pittsburgh of UPMC
Increased CSF NLRP3 but Not NLRP1 After Severe Traumatic Brain Injury in Children

T-08 Liao, George
University of Texas Health Science Center at Houston
The Post Traumatic Brain Injury Inflammasome and Response to Autologous Cell Therapy

T-09 Hinzman, Jason
University of Cincinnati
Inverse Neurovascular Coupling to Cortical Spreading Depolarizations in Severe Brain Trauma

T-10 Blaya, Meghan
University of Miami Miller School of Medicine
Genetically-Modified Neural Progenitor Cell Transplantation for the Treatment of Traumatic Brain Injury

T-11 Morioka, Kazuhito
University of California, San Francisco
Early Hindlimb Unloading Produces Maladaptive Plasticity that Limits Functional Recovery after Spinal Cord Injury (SCI)

T-12 Swartz, Emily
Pennsylvania State College of Medicine
Increased Nodose Ganglion Expression of CCK, CCK-1r, and TRPV1 and the Pathophysiology of Vagal Afferent Dysfunction.

T-13 Huie, J. Russell
University of California, San Francisco
Peripheral Nociceptive Input Overdrives AMPA Receptor Activity to Produce Maladaptive Plasticity After Spinal Cord Injury (SCI)

T-14 Okada, Starlyn
University of Louisville
Neuroprotective Effects of Pam3-CSK4 in Spinal Cord Injury

T-15 Wu, Xiangbing
Indiana University-Purdue University Indianapolis
RhoA/Rho Kinase Regulates cPLA2 activation in Spinal Cord Neuronal Toxicity Induced By TNF-α and Glutamate

T-16 von Leden, Ramona
Uniformed Services University of the Health Sciences
18F-FDG PET Imaging of Rat Spinal Cord Injury Shows Depressed Glucose Uptake Correlating With Lesion Volume and Functional Recovery

T-17 Hawryluk, Gregory
University of California, San Francisco
Higher Mean Arterial Blood Pressures Following Human Spinal Cord Injury Correlate With the Greater Neurological Recovery

T-18 Daneshi Kohan, Ehsan
Simon Fraser University
The Effects Of Myelin Retraction And Detachment On Signal Conduction In A Computational Model Of Damaged Axons

T-19 Aceves, Miriam
Texas A&M Health Science Center & Texas A&M Institute for Neuroscience
NorBNI Dose-Dependently Blocks the Adverse Effects of Intrathecal Morphine Administration Following SCI

T-20 Dollé, Jean-Pierre
University of Pennsylvania
Axonal Stretch Injury Results in a Potential Redistribution of Phosphorylated Tau From Axons to the Soma and Dendrites

Poster Session A

3:00 - 4:00 pm - Monday, June 30

TBI NEUROCRITICAL CARE

A1-01 Yu, Mingkun 3:00 PM - 3:15 PM
Shanghai Changzheng Hospital
The Surgical Strategy of Penetrating Orbito-Cranial Combined Injuries from High Temperature Liquid plastic: Case Report

A1-02 Naik, Bhiken 3:15 PM - 3:30 PM
University of Virginia
he Intrathoracic Pressure Regulator Lowers Intracranial Pressure In Patients With Altered Intracranial Elastance: A Pilot

A1-03 Yang, Seung Ho 3:30 PM - 3:45 PM
St. Vincent's Hospital The Catholic University of Korea
Early and Late Tracheostomy after Decompressive Craniectomy for Severe Traumatic Brain Injury

A1-04 Xu, Zao 3:45 PM - 4:00 PM
Indiana University School of Medicine
Inflammation In Traumatic Brain Injury With Hemorrhagic Shock

A1-05 Kumar, Sai 3:00 PM - 3:15 PM
SFC Fluidics, Inc
Development of a Portable Cerebral Microdialysis Platform for Automated Inline Multianalyte Detection System

A1-06 Madden, Lori 3:15 PM - 3:30 PM
University of California, Davis
Validation of the IMPACT Prognostic Models

A1-07 Rhind, Shawn 3:30 PM - 3:45 PM
DRDC Toronto
Modulation of Inflammatory Cytokine Balance by Sympathetic Nervous System Activation After Traumatic Brain Injury

A1-08 Brophy, Gretchen 3:45 PM - 4:00 PM
Virginia Commonwealth University
Multimodality Monitoring of Platelet Function in Traumatic Brain Injury Patients with Trauma Induced Coagulopathy

A1-09 Schneider, Eric 3:00 PM - 3:15 PM
Johns Hopkins University
Trends In Emergency Department Treatment Of Sport-Related Traumatic Brain Injury, 2006-2011

A1-10 Vavilala, Monica 3:15 PM - 3:30 PM
University of Washington
Acute Care Clinical Indicators Associated with Discharge Outcomes in Children with Severe Traumatic Brain Injury

A1-11 Goodman, Clay 3:30 PM - 3:45 PM
Baylor College of Medicine
Plasma and Cerebrospinal Fluid Erythropoietin Concentrations Following Erythropoietin Administration in Traumatic Brain Injury

A1-12 Oshio, Kotaro 3:45 PM - 4:00 PM
St. Marianna University School of Medicine
What Will You See In Intracranial Pressure Waveform Analysis?

A1-13 Brolliar, Sarah 3:00 PM - 3:15 PM
University of Washington
Factors Associated with Clinician Adherence to Pediatric Traumatic Brain Injury Guidelines: A Qualitative Study

A1-14 Alali, Aziz 3:15 PM - 3:30 PM
University of Toronto
Comparative Study of Outcome Measures and Analysis Methods for Traumatic Brain Injury Trials

A1-15 Tubi, Meral 3:30 PM - 3:45 PM
University of California Los Angeles
High Incidence of Delayed Seizures in Severe TBI Patients

A1-16 Schur, Solon 3:45 PM - 4:00 PM
McGill University
Decompressive Craniectomy In Traumatic Brain Injury: Determining Optimal Flap Size For Better Intracranial Pressure Control

A1-17 Puccio, Ava 3:00 PM - 3:15 PM
University of Pittsburgh
Brain Tissue Oxygenation And 3, 6-Month Neurological Outcome In Severe Traumatic Brain Injury

A1-18 Wolahan, Stephanie 3:15 PM - 3:30 PM
University of California Los Angeles
Influence Of Systemic Glucose On Ketogenic Metabolites

A1-19 Krishnamoorthy, Vijay 3:30 PM - 3:45 PM
University of Washington
The Indo-US Collaborative Head Injury and Adherence to Guidelines (CHIRAG) Project: Outcomes and Feasibility

A1-20 Bauer, Joshua 3:45 PM - 4:00 PM
University of Pittsburgh School of Medicine
Neurophysiological Testing for Long-Term Prognosis in Severe Traumatic Brain Injured Patients

A1-21 Nelson, Neta 3:00 PM - 3:15 PM
Besins Healthcare/ BHR Pharma, LLC
Lessons in Critical Care Research from a Global Phase 3 Trial of Progesterone in Patients with Severe TBI

A1-22 Kuzibaev, Jamshid 3:15 PM - 3:30 PM
Republican Research Center of Emergency Medicine
Treatment Of Refractory Intracranial Hypertension In Patients With Traumatic Intracranial Using Decompressive Craniectomy

TBI IMAGING

A2-01 Szu, Jenny 3:00 PM - 3:15 PM
University of California, RiversideMonitoring Mild Traumatic Brain Injury With Polarization-Sensitive Optical Coherence Tomography

A2-02 Wong, Yong Chiat 3:15 PM - 3:30 PM
DSO National Laboratories
White Matter Injury In A Rodent Model Of Blast Injury

A2-03 Yoder, Karmen 3:30 PM - 3:45 PM
Indiana University School of Medicine
Using PET to Detect Changes In Brain Blood Blow And Metabolism After Controlled Cortical Impact In Mice

A2-04 Tong, Karen 3:45 PM - 4:00 PM
Loma Linda Univ. Medical Center
Acute and 1 Year Follow-up MRI of Traumatic Hemorrhagic Brain Lesions after Moderate/Severe Pediatric TBI

A2-05 Tong, Karen 3:00 PM - 3:15 PM
Loma Linda Univ. Medical Center
Acute Susceptibility-Weighted MRI of Hemorrhagic Brain Lesions and One-Year Neuropsychologic Outcomes after Pediatric TBI

A2-06 Pronger, Angela 3:15 PM - 3:30 PM
Uniformed Services University of the Health Sciences
Mulitimodal Neuroimaging with Hypercapnia to Monitor Cerebrovascular Function after Traumatic Brain Injury and Evaluate Treatment

A2-07 Dodd, Andrew 3:30 PM - 3:45 PM
The Mind Research Network/Lovelace Biomedical and Environmental Research Institute
Multisensory Cognitive Control in an fMRI study of mTBI

A2-08 Watts, Lora 3:45 PM - 4:00 PM
University of Texas Health Science Center San Antonio
Manganese Enhanced MRI Following Traumatic Brain Injury

A2-09 Watts, Lora 3:00 PM - 3:15 PM
University of Texas Health Science Center San Antonio
MRI Reveals Widespread Disruptions In CBF And Vascular Reactivity Following Focal TBI

A2-10 DeGraba, Thomas 3:00 PM - 3:15 PM
National Intrepid Center of Excellence
Resting-State Brain Activity In Mild TBI Patients With High Versus Low Post-Traumatic Stress Disorder Symptom Severity

A2-11 Harris, Neil 3:30 PM - 3:45 PM
University of California Los Angeles
Network-Based Analysis of Structural Connectivity Reveals Altered Brain Organization after Experimental Brain Injury

A2-12 Harris, Neil 3:45 PM - 4:00 PM
University of California Los Angeles
Temporal Alterations In Functional Connectivity After Experimental Traumatic Brain Injury

A2-13 Afzal, Mariam 3:00 PM - 3:15 PM
Center for Neuroscience and Regenerative Medicine (CNRM)
Recruitment, Screening, and Classification of Acute TBI: Advantages of a Multi-Pathway Screening Protocol

Poster Session A

3:00 - 4:00 pm - Monday, June 30

A2-14 Magrath, Elizabeth 3:15 PM - 3:30 PM
Center for Neuroscience and Regenerative Medicine (USUHS)
Characterizing TBI Radiology Reads Using the Annotation and Image Markup Platform

A2-15 Kou, Zhifeng 3:30 PM - 3:45 PM
Wayne State University
Connectome-Scale Assessments of Structural and Functional Connectivity in Mild Traumatic Brain Injury at the Acute Stage

A2-16 Tremblay, Sebastien 3:45 PM - 4:00 PM
McGill University
Diffuse White Matter Tract Anomalies In Aging But Clinically Normal Retired Athletes With A History Of Sports-Related Concussions

A2-17 Holshouser, Barbara 3:00 PM - 3:15 PM
Loma Linda University
Early MRI Findings and 1-Year Outcomes in Pediatric Complicated Mild TBI

A2-18 Tu, Tsang-Wei 3:15 PM - 3:30 PM
National Institute of Health
CEST-MRI Is Sensitive In Non-Invasive Detection Of Glucose, Lactate, And Glutamate+Glutamine Interrelation In Mild Close Head TBI

A2-19 Hosomi, Sanae 3:30 PM - 3:45 PM
Osaka University Graduate School of Medicine
TSPO-PET Imaging After Traumatic Brain Injury In Mice

A2-20 Failla, Michelle 3:45 PM - 4:00 PM
University of Pittsburgh
Post-TBI Alterations In Fronto-Limbic Morphometry Are Associated With Depression

A2-21 Diaz-Arrastia, Ramon 3:00 PM - 3:15 PM
Center for Neuroscience and Regenerative Medicine
Cerebrovascular Dysfunction After Traumatic Brain Injury: Assessment With MRI And NIRS

A2-22 Shukla, Dinesh 3:15 PM - 3:30 PM
Uniformed Services University
Correlative MR And PET-FDG Imaging Of Lesion And Contralateral Cortex In Controlled Cortical Impact Brain Injury

A2-23 Parekh, Mansi 3:15 PM - 3:30 PM
Stanford University
Baseline Alterations Of Medial Temporal Lobe Substructures In Contact-Sport Athletes

A2-24 Puccio, Ava 3:45 PM - 4:00 PM
University of Pittsburgh
Quantifying White Matter Injury in Traumatic Brain Injury with High Definition Fiber Tracking

A2-25 Veeramuthu, Vigneswaran 3:00 PM - 3:15 PM
University of Malaya
Diffused Tensor Imaging Metrics In Acute Mild Traumatic Brain Injury And Its Correlation With Early Neuropsychological Impairment

A2-26 Dempsey, Alison 3:15 PM - 3:30 PM
National Institute of Health
MRI Targeted Pathology of Acute TBI

A2-27 McEntee, Julie 3:30 PM - 3:45 PM
Henry M. Jackson Foundation
Cross-Sectional Volumetric Comparison Of Mild And Moderate Traumatic Brain Injury

A2-28 Toth, Arnold 3:45 PM - 4:00 PM
University of Pécs
Lateral Ventricle Volume Asymmetry Predicts Midline Shift in Severe Traumatic Brain Injury

SCI MODELING / IMAGING

A3-01 Wu, Junfang 3:00 PM - 3:15 PM
University of Maryland, School of Medicine
Isolated Thoracic Spinal Cord Contusion In Mice Induces Cognitive And Emotional Behavior Impairments

A3-02 Callahan, Alison 3:15 PM - 3:30 PM
Stanford University
Minimum Information About a Spinal Cord Injury Experiment (MIASCI): Concepts and integration with the RegenBase Ontology

A3-03 Nielson, Jessica 3:30 PM - 3:45 PM
University of California San Francisco
Data-Driven Discovery Of Syndromic Efficacy For Preclinical Drug Trials In Cervical Spinal Cord Injury

A3-04 Haefeli, Jenny 3:45 PM - 4:00 PM
UCSF Brain and Spinal Injury Center
Towards Preclinical Sensory Common Data Elements In Spinal Cord Injury

A3-05 Zakszewski, Elizabeth 3:00 PM - 3:15 PM
The Medical College of Wisconsin
Advanced MRI Of The Rat Cervical Spine Following Thoracic Contusion SCI

TBI BIOMARKERS

A4-01 Lyeth, Bruce 3:00 PM - 3:15 PM
University of California, Davis
GFAP Fragment Biomarkers After TBI: Evidence For Acute Astrocyte Pathology

A4-02 Shear, Deborah 3:15 PM - 3:30 PM
Walter Reed Army Institute of Research
Delayed Consciousness, Sensory-Motor Deficits, And GFAP Levels In Repeated Concussive Impact.

A4-03 Wang, Kevin 3:30 PM - 3:45 PM
University of Florida
Plasma Anti-GFAP Autoantibody Levels During Acute And Chronic Phases Of TBI - A TRACK-TBI Pilot Study

A4-04 Geddes, James 3:45 PM - 4:00 PM
University of Kentucky
Brain Injury Screening by Ocular Analysis (BISON)

A4-05 Chandran, Raghavendar 3:00 PM - 3:15 PM
Henry M. Jackson Foundation/USUHS
Serum MicroRNA Signatures of Closed Head Injury in Mice: A Potential Biomarker for Mild Traumatic Brain Injury

A4-06 Brophy, Gretchen 3:15 PM - 3:30 PM
Virginia Commonwealth University
Microtubule-Associated Protein 2 (MAP2) CSF Biokinetic Characteristics Are Associated with Poor Outcomes in Severe TBI Patients

A4-07 Bashirelahi, Kylee 3:30 PM - 3:45 PM
Uniformed Services University
Determining The Feasibility Of Using Heart-Rate Variability For The Identification Of Mild TBI In Asymptomatic Participants

A4-08 Kumar, Sai 3:45 PM - 4:00 PM
SFC Fluidics, Inc
Immuno-Chain Reaction: A Novel Ultrasensitive Assay for Rapid Triaging of Brain Injury

A4-09 Wanner, Ina 3:00 PM - 3:15 PM
University of California Los Angeles
Human Astroglial Markers Are Defined By Release Mechanisms And Are Elevated In TBI Patients' CSF And Serum

A4-10 Ritter, Anne 3:15 PM - 3:30 PM
University of Pittsburgh
GFAP Autoantibody Developmental Trajectories after TBI: Characterization and Associations with Inflammatory markers

A4-11 Glenn, Thomas 3:15 PM - 3:30 PM
University of California Los Angeles
Metabolomic Analysis Of Biofluids From Patients With Severe Traumatic Brain Injury: Influence Of Cerebral Lactate Supplementation

A4-12 Yue, John 3:45 PM - 4:00 PM
University of California, San Francisco
C-Reactive Protein Augments the Diagnostic Value of Glial Fibrillary Acidic Protein in Detecting Acute CT Intracranial Pathology

A4-13 Crawford, Fiona 3:00 PM - 3:15 PM
The Roskamp Institute, Inc.
Plasma Lipidomic TBI Biomarker Profiles - Translation From Mouse To Human

Poster Session A

3:00 - 4:00 pm

A4-14 Diaz-Arrastia, Ramon 3:15 PM - 3:30 PM
Center for Neuroscience and Regenerative Medicine
Multi-Analyte Biomarker Panel Predicts Functional Outcome 6 Months After Traumatic Brain Injury.

A4-15 Lifshitz, Jonathan 3:30 PM - 3:45 PM
Barrow Neurological Institute at Phoenix Children's Hospital
Extracellular Matrix Biomarkers Are Severity Dependent And Regional Specific In Experimental Diffuse Brain Injury

A4-16 Bhomia, Manish 3:45 PM - 4:00 PM
Henry M Jackson Foundation/ USUHS S
Identification Of A Putative Panel Of Serum Micrornas For Diagnosis Of Human Traumatic Brain Injury

A4-17 LaPlaca, Michelle 3:00 PM - 3:15 PM
Georgia Institute of Technology/ Emory University
Lipidomic Profiling of Serum for the Development of Blood Based Biomarkers for Traumatic Brain Injury

TBI COGNITIVE FUNCTION / DEFICITS

A5-01 Bachstetter, Adam 3:00 PM - 3:15 PM
University of Kentucky
Closed Head Injury Enhances Cognitive Deficits And Disrupts The Resolution Of The Glia Response In An Alzheimer's Mouse Model

A5-02 Papesh, Melissa 3:15 PM - 3:30 PM
Portland VAMC
Blast Exposure Impairs The Brain's Ability To Modulate Sensitivity To Sensory Information: Evidence From The Veteran Population

A5-03 Chen, Zhiyong 3:30 PM - 3:45 PM
Walter Reed Army Institute of Research
Application of an Active Avoidance Task in Detecting Cognitive Deficits Following Penetrating Ballistic-like Brain Injury

A5-04 Kemppainen, Samuli 3:45 PM - 4:00 PM
NordLab
The Incidence of Traumatic Brain Injury in the County of Kainuu, Finland: The Kainuu TBI Cohort

A5-05 Pardini, Jamie 3:00 PM - 3:15 PM
University of Pittsburgh Medical Center
Observed Differences Between Athletes With and Without ADD At Baseline and Acute Post-Concussion Assessment

A5-06 Serpa, Rebecka 3:15 PM - 3:30 PM
University of California Los Angeles
Repeat Concussions in Female Adolescent Rats Decrease Social Interactions

Poster Session B

4:00 - 5:00pm - Monday, June 30

TBI REHABILITATION / RECOVERY

B1-01 Ranes, Bethany 4:00 PM - 4:15 PM
U.S. Army Aeromedical Research Laboratory
Evaluation of The Military Functional Assessment Program: Assessment of The Construct Validity Using Archived Clinical Data

B1-02 Shetty, Teena 4:15 PM - 4:30 PM
Hospital for Special Surgery
Barriers To Recovery After Concussion

B1-03 Kwon, Tae Gun 4:30 PM - 4:45 PM
Sungkyunkwan University School of Medicine
Effects of Dual Mode Non Invasive Brain Stimulation On Motor Function In Patients With Chronic Traumatic Brain Injury

B1-04 Conti, Alana 4:45 PM - 5:00 PM
Wayne State University/John D. Dingell VAMC
Mild Experimental TBI Increases Ethanol Consumption In The Delayed Post-TBI Period

B1-05 Nguyen, Anthony 4:00 PM - 4:15 PM
The University of Texas at Dallas
Vagus Nerve Stimulation And Nonparetic Limb Training Modify Stroke Recovery

B1-06 Greif, Taylor 4:15 PM - 4:30 PM
DePaul University
Effectiveness of The SLICE Concussion Education Program For Chicago Youth

B1-07 DeGraba, Thomas 4:30 PM - 4:45 PM
National Intrepid Center of Excellence
Neuroendocrine And Nutrition Status In Active Duty Service Members With Mtbi And Psychological Health Diagnosis

B1-08 Thompson, Floyd 4:45 PM - 5:00 PM
Malcolm Randall VAMC
Dose Response Effects of Acute Admistritation of Intrathecal Baclofen (ITB) On TBI-Induced Spasticity

B1-09 Thompson, Floyd 4:00 PM - 4:15 PM
Malcolm Randall VAMC
Therapeutic TMS Reduces TBI Spasticity, Anxiety, And Pain

B1-10 Salois, Garrick 4:15 PM - 4:30 PM
Saginaw Valley State University
Combining Enriched Environment, Progesterone, And Embryonic Neural Stem Cell Therapy Improves Recovery Following Brain Injury

B1-11 Lawson, Ben 4:30 PM - 4:45 PM
USAARL
Identification of Military Occupations Most Likely To Suffer Mild Traumatic Brain Injury (Mtbi) And Related Sensory Injuries.

B1-12 Pruitt, David 4:45 PM - 5:00 PM
The University of Texas at Dallas
Pairing Vagus Nerve Stimulation With Rehabilitative Training Enhances Functional Recovery After Traumatic Brain Injury

B1-13 Banfield, Joanne -
Sunnybrook Health Sciences Centre
Canadian Sport For Life: Are We Missing The Vaccine For Injury?

B1-14 Micci, Maria-Adelaide 4:15 PM - 4:30 PM
UTMB
Impaired Neurogenesis In A Rat Model of Traumatic Brain Injury

B1-15 Bondi, Corina 4:30 PM - 4:45 PM
University of Pittsburgh
Environmental Enrichment Restores Cognitive Performance In An Attentional Set-Shifting Test After Traumatic Brain Injury

B1-16 Zeiger, Max 4:45 PM - 5:00 PM
University of California Los Angeles
Longitudinal Recovery of Reaction Time In Acute And Chronic Concussion Patients

B1-17 Rabinowitz, Amanda 4:00 PM - 4:15 PM
University of Pennsylvania School of Medicine
Gender Differences In Symptom Report Following Mild TBI In Adolescents And Young Adults Depend On Age

B1-18 Thomas, Theresa 4:15 PM - 4:30 PM
University of Arizona College of Medicine - Phoenix
Verification of Circuit-Directed Rehabilitation Paradigm For Brain Injury-Induced Circuit Reorganization

B1-19 Yue, John 4:30 PM - 4:45 PM
University of California, San Francisco
Incidence of Outpatient Follow-Up Services In Functionally-Recovered Mild TBI Patients

B1-20 Veeramuthu, Vigneswaran 4:45 PM - 5:00 PM
University of Malaya
Attention, Memory And Executive Function Deficits In Patients With Complicated vs Uncomplicated Mild Traumatic Brain Injury

B1-21 C. Bourassa, Marie-Eve 4:00 PM - 4:15 PM
Université du Québec à Montréal
Attenuated Electrophysiological Response To Feedback Following Sports Concussions

B1-22 Curley, Kenneth 4:15 PM - 4:30 PM
US Army Medical Research and Materiel Command
Federal Coordination For Traumatic Brain Injury Research: The National Research Action Plan

Poster Session B

4:00 - 5:00pm - Monday, June 30

SCI REPAIR/CELL TRANSPLANT/RETRAIN

B2-01 Hyun, Jung Keun 4:00 PM - 4:15 PM
Dankook Univ
Mesoporous Silica Nanoparticles Can Deliver PTEN Inhibitor And Enhance Neuronal Regeneration Effectively

B2-02 Kim, Jong-Wan 4:15 PM - 4:30 PM
Department of Nanobiomedical Science
Directly Reprogrammed Neural Stem Cells Enhance Functional Recovery Following Spinal Cord Injury In Rats

B2-03 Jennifer, Brown 4:30 PM - 4:45 PM
Burke-Cornell Medical Research Institute
Using Transcription Factors To Promote The Survival of Transplanted Cells For Spinal Cord Injury Repair.

B2-04 Ashki, Negin 4:45 PM - 5:00 PM
University of South Carolina
Mir-21 Overexpression Depletes PTEN And Increases Axonal Phospho-S6 [withdrawn]

B2-05 Moonen, Gray 4:00 PM - 4:15 PM
University of Toronto
Development of A Lumbar Spinal Cord Injury Model To Examine The Therapeutic Potential of Transplanting Neuronally Induced NSPCS

B2-06 Awai, Lea 4:15 PM - 4:30 PM
Balgrist University Hospital
Domains of Neural Control of Walking In Human Spinal Cord Injury

B2-07 Keller, Anastasia 4:30 PM - 4:45 PM
University of Louisville
Hindlimb Muscle Stretch Reduces Locomotor Function After A Spinal Cord Injury: Acute And Chronic Time Points

B2-08 Silva, Nuno 4:45 PM - 5:00 PM
Life and Health Sciences Research Institute (ICVS)
Improving Locomotion In Spinal Cord Injured Rats: A Bioengineering Approach

B2-09 Vawda, Reaz 4:00 PM - 4:15 PM
University Health Network
Umbilical Cord Matrix Cell Secretome Reduces Vascular Permeability & Lesion Volume After Traumatic Spinal Cord Injury

B2-10 Peduzzi Nelson, Jean 4:15 PM - 4:30 PM
Wayne State School of Medicine
Functional Improvement With Intranasally-Delivered Human Olfactory Stem Cells And Exercise And Enrichment In Spinal Cord Injury

TBI COGNITIVE FUNCTION / DEFICITS

B3-01 Garcia, Roberto 4:00 PM - 4:15 PM
Baylor College of Medicine
Acute Stress Complicating Mild Traumatic Brain Injury In Rodents

B3-02 Chou, Austin 4:15 PM - 4:30 PM
University of California - San Francisco
Effect of Aging On Cognitive Outcome And Neuroinflammatory Response After Traumatic Brain Injury

B3-03 Chou, Austin 4:30 PM - 4:45 PM
University of California - San Francisco
Frontal Lobe Injury And Prefrontal Cortex-Dependent Functions In Mice

B3-04 Vogel, Edward 4:45 PM - 5:00 PM
Columbia University in the City of New York
Primary Blast Injury Eliminates Long-Term Potentiation In Rat Organotypic Hippocampal Slice Cultures

B3-05 Folmer, Robert 4:00 PM - 4:15 PM
Portland VA Medical Center
Electrophysiological Evidence of Auditory And Cognitive Dysfunction In Veterans Exposed To High-Intensity Blasts

B3-06 Wagner, Amy 4:15 PM - 4:30 PM
Univ Pittsburgh
Visual Priming Enhances The Effects of Non-Spatial Cognitive Rehabilitation Training On Spatial Learning After Experimental TBI

B3-07 DeGraba, Thomas 4:00 PM - 4:15 PM
National Intrepid Center of Excellence
Differences In Symptom Severity In Mtbi Patients With And Without PTSD

B3-08 Ghajar, Jamshid 4:45 PM - 5:00 PM
Brain Trauma Foundation
Controlling Confounding Effects In Mtbi Visual Tracking Assessment

B3-09 LaPlaca, Michelle 4:00 PM - 4:15 PM
Georgia Institute of Technology/ Emory University
Display Enhanced Testing of Cognitive Impairment And Mild Traumatic Brain Injury (DETECT): A Novel Tool For Concussion Assessment

B3-10 Vonder Haar, Cole 4:15 PM - 4:30 PM
University of British Columbia
Effects of Frontal TBI On Simple Response Requirements In Rats

TBI PEDIATRIC

B4-01 Moore, Megan 4:00 PM - 4:15 PM
University of Washington
Acute Care After Pediatric Traumatic Brain Injury: A Qualitative Study of The Family Perspective

B4-02 Urban, Karolina 4:15 PM - 4:30 PM
University of Calgary
PLAYGAME: A Randomized, Double Blind, Placebo Controlled Trial of Melatonin For The Treatment of Post Concussion Syndrome In Youth

B4-03 Hall, Larry 4:30 PM - 4:45 PM
Children's Healthcare of Atlanta
Effect of A Community Education Program On Pediatrician's Management of Concussions

B4-04 Mahuvakar, Alpa 4:45 PM - 5:00 PM
University of California San Francisco
Matrix Metalloproteinases As Therapeutic Targets For The Injured Pediatric Brain

B4-05 Ewing-Cobbs, Linda 4:00 PM - 4:15 PM
University of Texas Health Science Center at Houston
Emotion Processing Following Pediatric Traumatic Brain Injury

B4-06 Furukawa, Daisuke 4:15 PM - 4:30 PM
David Geffen School of Medicine at UCLA
Sleep Disturbance In Sports Related Concussions In Children

B4-07 Jackson, Travis 4:30 PM - 4:45 PM
University of Pittsburgh
Effect of TBI On RNA Binding Motif 5 (RBM5) And 3 (RBM3) Protein Expression In The Developing Rat Brain

B4-08 Fidan, Emin 4:45 PM - 5:00 PM
University of Pittsburgh
Repetitive Mild Traumatic Brain Injury In The Immature Brain

B4-09 Switzer III, Robert 4:00 PM - 4:15 PM
NeuroScience Associates
Normal Background of Apoptosis In Juvenile Rats Used As Basis To Determine Induced Degeneration By The Neurotoxin MK-801

B4-10 Segal, Andrew 4:15 PM - 4:30 PM
University of California Los Angeles
Examining D-Cycloserine Administration Protocols In Developing Rats Following LFPI And Reducing Variability In pCaMKII Levels

B4-11 Merkel, Steven 4:30 PM - 4:45 PM
Temple University School of Medicine
Moderate Traumatic Brain Injury (TBI) In Adolescent Mice Enhances Cocaine-Induced Place Preference

B4-12 Scafidi, Susanna 4:45 PM - 5:00 PM
Johns Hopkins University School of Medicine
Acetyl-L-Carnitine Improves Metabolic Dysfunction And Behavioral Outcome After Traumatic Brain Injury In Immature Rat

B4-13 Semple, Bridgette 4:00 PM - 4:15 PM
University of California, San Francisco
Long-Term Behavioral Consequences Emerge Over Time After Concussive Injuries At Adolescence

B4-14 Urban, Karolina 4:15 PM - 4:30 PM
University of Calgary
Pediatric Post-Concussion Symptoms Are Associated With Reduced Cortical Communication As Detected With Near-Infrared Spectroscopy

Poster Session B

4:00 - 5:00pm - Monday, June 30

B4-15 Ellis, Timothy 4:30 PM - 4:45 PM
Midwestern University
Midline Fluid Percussion Injury In The Developing Rodent Results In Diffuse Injury And Deviation of The Neurovascular Unit

B4-16 Biswas, Chaitali 4:45 PM - 5:00 PM
University of California, Los Angeles (UCLA)
Electrophysiological Signatures of Juvenile Mild Traumatic Brain Injury During Novel Object Recognition

B4-17 Rossi, Janet 4:00 PM - 4:15 PM
LSUHSC/Children's Hospital
ISG15 An Early Stimulus To Blood-Brain Barrier Disruption After Traumatic Brain Injury In Immature Mice

B4-18 Schober, Michelle 4:15 PM - 4:30 PM
University of Utah
Neuroprotective Mechanisms of Docosahexaenoic Acid In Rat Pups After Traumatic Brain Injury

B4-19 DeMaster, Dana 4:30 PM - 4:45 PM
UT Health Science Center at Houston
Memory And The Hippocampal Formation Following Pediatric Traumatic Brain Injury

B4-20 Emery, Carolyn 4:45 PM - 5:00 PM
University of Calgary
The Effect of Body Checking And Head Contact Rule Policy Changes On Concussion Risk In Youth Ice Hockey Players

B4-21 Mayer, Andrew 4:00 PM - 4:15 PM
Mind Research Network
Gray Matter Abnormalities In Pediatric Mild Traumatic Brain Injury

B4-22 Ewing-Cobbs, Linda 4:15 PM - 4:30 PM
University of Texas Health Science Center at Houston
Salivary Biomarkers of Stress Reactivity Following Pediatric Traumatic Brain Injury

B4-23 Duhaime, Ann-Christine 4:30 PM - 4:45 PM
Massachusetts General Hospital
Pediatric Patients In The TRACK TBI Trial - Testing Common Data Elements In Children

B4-24 Piao, Chunshu 4:45 PM - 5:00 PM
Ann & Robert H. Lurie Children's Hospital of Chicago
Thrombin And Protease-Activated Receptor-1 Are Activated In Intractable Epilepsy In Children

B4-25 Mills, Brianna 4:00 PM - 4:15 PM
University of Washington
Facility-Level Characteristics And Pediatric In-Hospital Mortality Following Severe Traumatic Brain Injury

B4-26 Todani, Masaki 4:15 PM - 4:30 PM
Virginia Commonwealth University
The Juvenile Rat Brain Shows Increased Vulnerability To Low Impact Repetitive Injury Over Prolonged Posttraumatic Intervals

B4-27 Holshouser, Barbara 4:30 PM - 4:45 PM
Loma Linda University
Acute MRS And DTI Findings After Moderate/Severe Pediatric TBI

B4-28 Dennis, Emily 4:45 PM - 5:00 PM
USC Keck School of Medicine
Longitudinal Tract-Based Analysis of Callosal Disruption In Moderate/Severe Pediatric Traumatic Brain Injury

B4-29 Greco, Tiffany 4:00 PM - 4:15 PM
University of California Los Angeles
Adolescent Repeat Traumatic Brain Injury Causes Acute Cell Death And Long-Term Inflammation In The Anterior Pituitary of Rats

B4-30 Kannan, Nithya 4:15 PM - 4:30 PM
University of Washington
Hypotension Patterns And Vasopressor Choice After Severe Traumatic Brain Injury Across Five Pediatric Trauma Centers

B4-31 Choe, Meeryo 4:30 PM - 4:45 PM
University of California Los Angeles
Postural Orthostatic Tachycardia Syndrome After Mild TBI

TBI SECONDARY INJURY

B5-01 Armstrong, Regina 4:00 PM - 4:15 PM
USUHS
Progression of Myelin Pathology In TBI With Traumatic Axonal Injury of The Corpus Callosum

B5-02 Kibayashi, Kazuhiko 4:15 PM - 4:30 PM
School of Medicine, Tokyo Women's Medical University
Decreased Serotonin Transporter Expression After Traumatic Brain Injury In A Rat Controlled Cortical Impact Model

B5-03 Goodus, Matthew 4:30 PM - 4:45 PM
Rutgers University
Leukemia Inhibitory Factor Deficient Mice Have An Increased Vulnerability To Mild Prediatric Traumatic Brain Injury

B5-04 McGuire, Jennifer 4:45 PM - 5:00 PM
University of Cincinnati
Acute Alterations In Glutamate Neurotransmission After Concussive Brain Injury

B5-05 Arun, Peethambaran 4:00 PM - 4:15 PM
Walter Reed Army Institute of Research
Blast Exposure Phosphorylates Tau Preferentially At Serine396, Which Can Trigger Alzheimer's-Like Pathology

B5-06 Cartagena, Casandra 4:30 PM - 4:45 PM
Walter Reed Army Insitute of Research
Prolonged Increases In 22 Kda Tau Fragment Following Penetrating TBI

Poster Sessions A & B

Author Set-Up Time:
Sunday beginning at 12:00 pm

Poster Viewing Times:
Posters should remain on display from set up until 6:00 pm on Monday

Group A Presentations
Monday from 3:00 to 4:00 pm

Group B Presentations
Monday from 4:00 to 5:00 pm

Wine & Cheese Open Session:
Monday from 5:00 to 6:00 pm

Author Removal Time:
Monday from 6:00 – 6:30 pm

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

Poster Sessions C & D

Author Set-Up Time:
Monday beginning at 6:30 pm

Poster Viewing Times:
Posters should remain on display from set up until 8:00 am on Wednesday

Group C Presentations
Tuesday from 3:00 to 4:00 pm

Group D Presentations
Tuesday from 4:00 to 5:00 pm

Wine & Cheese Open Session:
Tuesday from 5:00 to 6:00 pm

Author Removal Time:
Wednesday from 8:00 – 10:30 am

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

Neurotrauma 2014 Agenda
Tuesday, July 1

7:00 am - 5:00 pm	Neurotrauma Registration Desk Open	Yerba Buena Foyer
7:00 am - 7:45 am	Continental Breakfast / Visit Exhibits / Open Poster Viewing [0.75 CME]	Yerba Buena 7/8
7:00 am - 7:45 am	**NNS Business Meeting** *Open to all NNS members*	Nob Hill A-B-C
7:50 am - 8:00 am	President's Welcome - Jacqueline Bresnahan PhD, UCSF	Yerba Buena 9
8:00 am - 10:00 am	**Synaptogenesis After Neurotrauma** [2.00 CME] Chair: John Povlishock, PhD; Virginia Commonwealth University	Yerba Buena 9
8:00-8:40	Synaptic and Network Plasticity Karunesh Ganguly, PhD; University of California San Francisco	
8:40-9:20	Synaptogenesis Forms New Circuits in the Diffuse-Injured Brain Jonathan Lifshitz, PhD; Barrow Neurological Institute at Phoenix Children's Hospital	
9:20-10:00	Impact of Astrogliosis on New Circuit Formation and Synaptogenesis After SCI Michael Sofroniew, PhD; University of California Los Angeles	
10:00 am - 10:30 am	Coffee Break & Visit Exhibits	Yerba Buena 7/8
10:30 am - 12:00 pm	**Pediatric TBI: A Legacy of Chronic Deficit** [1.50 CME] Chair: Harvey Levin, PhD; Baylor College of Medicine	Yerba Buena 1-6
10:30-11:00	The Emergence of Age-Dependent Social Deficits after Traumatic Injury to the Developing Brain Linda Noble, PhD; University of California San Francisco	
11:00-11:30	Social Cognition 15 Years Following Early Childhood Traumatic Brain Injury Vicki Anderson, PhD; Murdoch Children's Research Institute	
11:30-12:00	The Social Network After TBI: Social Outcome and the Brain Gerri Hanten, PhD; Baylor College of Medicine	
10:30 am - 12:00 pm	**Current Advances in Chronic TBI Cognitive Therapies** [1.50 CME] Chair: Coleen Atkins, PhD; University of Miami	Yerba Buena 9
10:30-11:00	Combined Therapeutic Paradigms After TBI: Are Two Better Than One? Anthony Kline, PhD; University of Pittsburgh	
10:30-11:00	Determining the Time Window for Successful Experience-Dependent Rehabilitation Grace Griesbach, PhD; University of California Los Angeles	
11:30-12:00	Harnessing Synaptic Plasticity Mechanisms for Chronic TBI Therapeutics Coleen Atkins, PhD; University of Miami	
10:30 am - 12:00 pm	**Innovation and Invention in Neurotrauma** [1.50 CME] Chair: Michelle LaPlaca, PhD; Georgia Tech / Emory University	Yerba Buena 10-15
10:30-11:00	Invention and Translation of Neurotechnologies: Observations of a Federal R&D Manager Col. Kenneth Curley, MD; US Army Medical Research and Materiel Command	
10:30-11:00	Biohybrid Systems for Neurotrauma: Ideas to Innovation Ranu Jung, PhD; Florida International University	
11:30-12:00	How to Be a Successful Innovator in Neurotrauma Ronald Hayes, PhD; Banyan Biomarkers Inc.	
12:00 pm - 1:30 pm	FREE TIME - LUNCH ON YOUR OWN	
12:00 pm - 1:30 pm	NNS Officers & Councilors Lunch *[By invitation only]*	Nob Hill C
1:30 pm - 3:00 pm	**Advances in Multimodal Imaging of TBI** [1.50 CME] Chair: John van Horn, PhD; University of Southern California	Yerba Buena 1-6
1:30-2:00	Multimodal Imaging Reveals the Link Between Early Metabolic Crisis and Cognitive Outcomes Following Traumatic Brain Injury Matthew Wright, PhD; University of California Los Angeles	
2:00-2:30	Computational Considerations in TBI Neuroimaging Data Analysis Guido Gerig, PhD; University of Utah	
2:30-3:00	Brain Atrophy Mapping in Traumatic Brain Injury Using Multimodal Neuroimaging Andrei Irimia, PhD; University of Southern California	

Neurotrauma 2014 Agenda
Tuesday, July 1

Tuesday

1:30 pm - 3:00 pm	**Repeat Concussions** [1.50 CME] Chair: Mayumi Prins, PhD; University of California Los Angeles	Yerba Buena 9
1:30-2:00	Repetitive Mild TBI in the Developing Brain Hulya Bayir, PhD; Safar Center for Resuscitation Research	
2:00-2:30	Repeat Concussions in Female Adolescent Rats Decrease Social Interactions Mayumi Prins, PhD; University of California Los Angeles	
2:30-3:00	Modeling Repetitive Concussions in Immature Mice Michael Whalen, PhD; Massachusetts General Hospital	
1:30 pm - 3:00 pm	**Cognitive Aging and TBI: The Role of Inflammation** [1.50 CME] Chair: Susanna Rosi, PhD; University of California San Francisco	Yerba Buena 10-15
1:30-2:00	Inflammaging: The Links Between Aging, Inflammation and Brain Structure and Function Joel Kramer, PhD; University of California San Francisco	
2:00-2:30	Aging, TBI and Inflammation: A Clinical Perspective Hilaire Thompson, PhD; University of Washington	
2:30-3:00	Innate Immune Response and Neuronal Function in the Aging Brain After TBI Susanna Rosi, PhD; University of California San Francisco	
3:00 pm - 3:45 pm	**Open Communications Session II: TBI** [0.75 CME] Chair: Kathryn Saatman, PhD; University of Kentucky	Yerba Buena 1-6
3:00-3:15	OC2.01 Blast Injury Exacerbates Neuropathology and Impairs Visual Function in a Transgenic APPswe-PSEN1dE9 Mouse Model of AD Matthew Harper, PhD; University of Iowa	
3:15-3:30	OC2.02 Efficient Estimation of Brain Strain Responses in Contact Sports Using a Pre-Computed Model Response Atlas Songbai Ji, PhD; Dartmouth College	
3:30-3:45	OC2.03 A Rabbit Model of Pediatric Traumatic Brain Injury Courtney Robertson, PhD; Johns Hopkins University	
3:00 pm - 3:45 pm	**Open Communications Session II: SCI** [0.75 CME] Chair: Caitlin Hill, PhD; Burke-Cornell Medical Research Institute	Yerba Buena 9
3:00-3:15	OC4.01 Vibration Exposure Limits for Neurotrauma Patients during Medical Transport: Overview Khalid Barazanji, PhD; U.S. Army Aeromedical Research Laboratory	
3:15-3:30	OC4.02 Disruption of Autophagy Flux Following Spinal Cord Injury in GFP-LC3 Reporter Mice Marta Lipinski, PhD; University of Maryland	
3:30-3:45	OC4.03 Inhibition of NOX2 Reduces Locomotor Impairment, Inflammation and Oxidative Stress After Spinal Cord Injury Kimberly Byrnes, PhD; Uniformed Services University	
3:00 pm - 3:45 pm	**Open Communications Session II: Clinical** [0.75 CME] Chair: Keith Tansey, MD, PhD; Emory University	Yerba Buena 10-15
3:00-3:15	OC6.01 Report of Longitudinal MRS and DTI after Moderate/Severe Pediatric TBI Barbara Holshouser, PhD; Loma Linda University	
3:15-3:30	OC6.02 Optimizing Neuromodulation for Walking in Human Incomplete Spinal Cord Injury Keith Tansey, MD, PhD; Emory University	
3:30-3:45	OC6.03 Intracranial Pressure Treatment Tailored to Transcranial Doppler-Derived Compliance & Perfusion Gregory Kapinos, MD; Hofstra University	
3:00 pm - 4:00 pm	**Poster Session II: C1-C3** [1.00 CME]	Yerba Buena 7/8
4:00 pm - 5:00 pm	**Poster Session II: D1-D2** [1.00 CME]	Yerba Buena 7/8
5:00 pm - 6:00 pm	**Wine & Cheese Open Poster Viewing II** [1.00 CME]	Yerba Buena 7/8
6:00 pm - 7:15 pm	FREE TIME - ON YOUR OWN	
7:15 pm - 7:30 pm	Bus Transportation to Pier 43½ for San Francisco Bay Cruise [Ticket Required]	
8:00pm - 10:00 pm	**San Francisco Bay Cruise** Sponsored by National Neurotrauma Society	San Francisco Pier 43½

Poster Session C

3:00 - 4:00 pm - Tuesday, July 1

SCI PROTECTION / SECONDARY INJURY

C1-01 Fandel, Thomas 3:00 PM - 3:15 PM
University of California, San Francisco
Matrix Metalloproteinases As A Therapeutic Target For Supporting Urologic Recovery In A Murine Model Of Spinal Cord Injury

C1-02 Crowdus, Carolyn 3:15 PM - 3:30 PM
University of Kentucky
Gene Expression Changes In Response To Selenium Diet In Spinal Cord Injured Rats

C1-03 Díaz-Galindo, María 3:30 PM - 3:45 PM
Universidad Autónoma de Aguascalientes
Effect Of A Gnrh Agonist On Locomotion, Gait And Spinal Cord Morphology In Rats With Spinal Cord Injury.

C1-04 Pan, Jonathan 3:45 PM - 4:00 PM
University of California San Francisco
Modulation Of Inflammatory Responses By Soluble TNF Receptor In A Rat Model Of Cervical Spinal Cord Injury (SCI)

C1-05 Radulovic, Maja 3:00 PM - 3:15 PM
Mayo Clinic
Kallikrein Cascades In Traumatic Spinal Cord Injury: Differential Roles In Axonopathy And Neuron Degeneration

C1-06 Dasari, Venkata Ramesh 3:15 PM - 3:30 PM
University of Illinois College of Medicine at Peoria
Modulation Of Matrix Metalloproteinases After Spinal Cord Injury Improves Functional Recovery Of Rats

C1-07 Sontag, Christopher 3:30 PM - 3:45 PM
University of California San Francisco
Pharmacologically Targeting L-Selectin Improves Outcomes Following Spinal Cord Injury.

C1-08 Liu, Nai-Kui 3:45 PM - 4:00 PM
Indiana University School of Medicine
Role Of Cpla2 In The Pathogenesis Of Spinal Cord Injury

C1-09 Huang, Zhihong 3:00 PM - 3:15 PM
Acorda Therapeutics
AC105 Increases Delivery Of Extracellular Magnesium To Injured Spinal Cord Tissue In Rats

C1-10 Pocratsky, Amanda 3:15 PM - 3:30 PM
University of Louisville School of Medicine
Conditional Silencing Of Adult Rat Spinal Locomotor Circuitry Induces Hopping

C1-11 Saigal, Rajiv 3:30 PM - 3:45 PM
University of California San Francisco
Induced Hypertension Does Not Improve Outcomes In Penetrating Spinal Cord Injury

TBI PROTECTION

C2-01 Tang, Huiling 3:00 PM - 3:15 PM
Emory University
Combination Therapy With Progesterone And Vitamin D Protects The Neurovascular Unit After Traumatic Brain Injury

C2-02 Dunkerson, Jacob 3:15 PM - 3:30 PM
Saginaw Valley State University
Combining Enriched Environment And Induced Pluripotent Stem Cell Therapy Restores Function Following Traumatic Brain Injury

C2-03 Zeng, Yaping 3:30 PM - 3:45 PM
UTMB
Traumatic Brain Injury Reduces Vascular Reactivity In Aging Rat Middle Cerebral Arteries

C2-04 Lu, Xi-Chun 3:45 PM - 4:00 PM
Walter Reed Army Institute of Research
A Combination Therapy Of Phenytoin And Ethosuximide Improved Therapeutic Benefits Against Post-Traumatic Nonconvulsive Seizures

C2-05 Wei, Guo 3:00 PM - 3:15 PM
WRAIR
Therapeutic Window For Selective Brain Cooling Following Penetrating Ballistic-Like Brain Injury In Rats

C2-06 Chen-Roetling, Jing 3:15 PM - 3:30 PM
Thomas Jefferson University
Selective Astrocyte Overexpression Of Heme Oxygenase-1 Is Protective After Intracerebral Hemorrhage

C2-07 Bramlett, Helen 3:30 PM - 3:45 PM
Univ. of Miami School of Med.
Dose-Response Evaluation Of Levetiracetam In The Miami Fluid Percussion Model Of Traumatic Brain Injury: An OBTT Consortium Study

C2-08 Dietrich, W. Dalton 3:45 PM - 4:00 PM
University of Miami Miller School of Medicine
Dose-Response Evaluation Of Simvastatin In The Miami Fluid Percussion Model Of Traumatic Brain Injury: An OBTT Consortium Study

C2-09 Caudle, Krista 3:00 PM - 3:15 PM
Walter Reed Army Institute of Research
Evaluation Of Levetiracetam In The WRAIR PBBI Model: Studies From The Operation Brain Trauma Therapy (OBTT) Consortium

C2-10 Caudle, Krista 3:15 PM - 3:30 PM
Walter Reed Army Institute of Research
Neuroprotective Effects Of Levetiracetam Requires Extended Treatment In A Rat Model Of Penetrating Ballistic-Like Brain Injury

C2-11 Bachstetter, Adam 3:30 PM - 3:45 PM
University of Kentucky
A Novel Small Molecule Anti-Cytokine Therapeutic Attenuates Downstream Cognitive Behavioral Deficits In A Mouse Model Of TBI

C2-12 Nishida, Hidetaka 3:45 PM - 4:00 PM
Texas A&M Health Science Center
Defining How TSG-6 Improves Long Term Memory After Traumatic Brain Injury In Mice

C2-13 Elmore, Brandy 3:00 PM - 3:15 PM
Souther Illinois University at Carbondale
A Comparative Evaluation Of Memantine And Topiramate: No Evidence Of Functional Recovery Following Traumatic Brain Injury

C2-14 Shear, Deborah 3:15 PM - 3:30 PM
Walter Reed Army Institute of Research
Evaluation Of Simvastatin In The WRAIR PBBI Model: Studies From The Operation Brain Trauma Therapy (OBTT) Consortium

C2-15 Bartnik Olson, Brenda 3:30 PM - 3:45 PM
Loma Linda University
Early Glucose Supplementation Following Controlled Cortical Impact Injury Does Not Alter Oxidative Metabolism 24 Hrs Post-Injury.

C2-16 Cartagena, Casandra 3:45 PM - 4:00 PM
Walter Reed Army Insitute of Research
Neuroprotective Effects Of Novel Therapeutic NNZ-2591 Following Penetrating TBI.

C2-17 McGuire, Laura 3:00 PM - 3:15 PM
University of Miami Miller School of Medicine
The Development Of Non-Convulsive Seizures Following Mild Traumatic Brain Injury With Mild Hyperthermia In The Rat

C2-18 Morganti, Josh 3:15 PM - 3:30 PM
University of California San Francisco
Differential Effects Of CX3CR1 Or CCR2 Deletion In Hippocampal Inflammatory Response Following Traumatic Brain Injury

C2-19 Adaikkalasamy, David 3:30 PM - 3:45 PM
University of Miami Miller School of Medicine
Pde4b Inhibition Rescues Chronic Memory Deficits Following Traumatic Brain Injury

C2-20 Weisz, Harris 3:45 PM - 4:00 PM
University of Texas Medical Branch
Effects Of Prophylactic Omega-3 Fatty Acid Treatment On TBI-Induced Microrna Expression

C2-21 Wilson, Nicole 3:00 PM - 3:15 PM
University of Miami Miller School of Medicine
Phosphodiesterase 4B Inhibition As A Therapeutic For Traumatic Brain Injury

Poster Session C

3:00 - 4:00 pm - Tuesday, July 1

C2-22 Lee, Sangmi 3:15 PM - 3:30 PM
University of California San Francisco
P75NTR Mediates Leukocyte Trafficking In The Brain After Traumatic Brain Injury (TBI) In Mice

C2-23 Sun, Dong 3:30 PM - 3:45 PM
Virginia Commonwealth University
The Effect Of 7, 8-Dihydroxyflavone (7,8-DHF) Following Traumatic Brain Injury

C2-24 Gowans, Amanda 3:45 PM - 4:00 PM
DePaul University
Transplanted Neurospheres From Genetically Modified Adult Bone Marrow After CCI: Effects On Injury Size And Transplant Survival

C2-25 Wynne, Karon 3:00 PM - 3:15 PM
University of Texas Medical Branch
Investigation Of The Effects Of Carboxyfullerene Nanoparticles On The Cerebral Vasculature After Fluid Percussion Injury

C2-26 Khan, Mushfiquddin 3:15 PM - 3:30 PM
Medical University of South Carolina
The Emerging Role Of AMP-Activated Protein Kinase In TBI And Its Pharmacological Regulation By S-Nitrosoglutathione

C2-27 Jacobs, Kimberle 3:30 PM - 3:45 PM
Virginia Commonwealth University
Knockout Of Cyclophilin D Prevents Increased Intrinsic And Synaptic Neuronal Excitability After Mild Traumatic Brain Injury (Mtbi)

C2-28 Miller, Darren 3:45 PM - 4:00 PM
University of Kentucky
The Nrf2-ARE Pathway As A Therapeutic Target In Traumatic Brain Injury: Genetic And Pharmacological Approaches For Neuroprotection

C2-29 Sutton, Richard 3:00 PM - 3:15 PM
University of California Los Angeles
Effects Of Ethyl Pyruvate On Markers Of Oxidative Stress And Glycolytic Function After Traumatic Brain Injury

C2-30 Hoda, Md Nasrul 3:15 PM - 3:30 PM
Georgia Regents University
Remote Ischemic Preconditioning (Riprec) Protects From Traumatic Brain Injury (TBI)

C2-31 Ikonomovic, Milos 3:30 PM - 3:45 PM
University of Pittsburgh
Memantine Hydrochloride As A Therapy For Traumatic Brain Injury: A Preclinical Study Using The CCI Injury Model In Rats

C2-32 McDonald, Whitney 3:45 PM - 4:00 PM
University of California Los Angeles
Blocking Lysophosphatidic Acid (LPA) Increases Subventricular Zone Proliferation But Reduces Early Neuroblast Migration After TBI

C2-33 Marin, Miguel 3:00 PM - 3:15 PM
Baylor College of Medicine
Degeneration And Protection Of Axonal Sub Domains After Optic Nerve Crush

C2-34 Hook, Greg 3:15 PM - 3:30 PM
American Life Science Pharmaceuticals
The Cysteine Protease Cathepsin B Is A Key Drug Target And Cysteine Protease Inhibitors Are Potential Therapeutics For TBI

C2-35 Yin, Terry 3:30 PM - 3:45 PM
University of Iowa
Efficacy Of Neuroprotective Compound P7C3-S243 After Blast-Mediated Traumatic Brain Injury

TBI SECONDARY INJURY

C3-01 Glushakova, Olena 3:00 PM - 3:15 PM
Banyan Biomarkers, Inc.
Delayed Microbleeds And White Matter Damage After Experimental Traumatic Brain Injury

C3-02 Boone, Debbie 3:15 PM - 3:30 PM
University of Texas Medical Branch
Traumatic Brain Injury-Induced Micrornas Suppress Prosurvival Gene Expression

C3-03 Diamond, Matthew 3:30 PM - 3:45 PM
University of Pittsburgh
Adenosine Kinase Gene Associated With Post-Traumatic Epilepsy Development

C3-04 Wang, Yushan 3:45 PM - 4:00 PM
DRDC Suffield Research Centre
Differential Regulation Of The Akt Signaling Pathway In Rat Brain After Primary Blast Induced Traumatic Brain Injury

C3-05 Marquis, Andrew 3:00 PM - 3:15 PM
Purdue University
Endogenous Elevation Of Acrolein Following Acute Traumatic Brain Injury In Rats

C3-06 Johnson, David 3:15 PM - 3:30 PM
Walter Reed Army Institute of Research
Microrna Dysregulation Occurs At Acute Time Points After Penetrating Ballistic-Like Brain Injury

C3-07 Lucke-Wold, Brandon 3:30 PM - 3:45 PM
West Virginia University School of Medicine
Connecting Acute Neurotrauma To Chronic Traumatic Encephalopathy: The Role Of The Endoplasmic Reticulum Stress Response

C3-08 Hinzman, Jason 3:45 PM - 4:00 PM
University of Cincinnati
Spreading Depolarizations Mediate Glutamate Excitotoxicity In Development Of Acute Cortical Lesions

C3-09 Fujita, Motoki 3:00 PM - 3:15 PM
Yamaguchi University Hospital
High Mobility Group Box-1 (HMGB1) Expression In Oligodendrocytes Of Rats Subjected To Lateral Fluid Percussion Injury (LFPI)

C3-10 Macolino, Christine 3:15 PM - 3:30 PM
Thomas Jefferson University
Cortical Injury Modulates The Pain Pathway Partially Through Inducible Nitric Oxide Synthase

C3-11 Friess, Stuart 3:30 PM - 3:45 PM
Washington University at St. Louis
Increased Intracranial Pressure Following Controlled Cortical Impact Exacerbates White Matter Axonal Injury And Atrophy

C3-12 Carlson, Shaun 3:45 PM - 4:00 PM
University of Pittsburgh
Impaired Synaptic Vesicle Docking Is A Novel Contributor To Reduced Neurotransmission After Traumatic Brain Injury

C3-13 Dastgheyb, Raha 3:00 PM - 3:15 PM
Drexel University
Secondary Membrane Damage And The Potential For Membrane-Targeted Neuroprotection

C3-14 Leung, Lai Yee 3:15 PM - 3:30 PM
Walter Reed Army Institute of Research
Regional And Temporal Histopathological Changes Following Mild Concussive Brain Injury

C3-15 Leung, Lai Yee 3:30 PM - 3:45 PM
Walter Reed Army Institute of Research
Region-Specific Impairment Of Cerebral Mitochondrial Bioenergetics Following Penetrating Ballistic-Like Brain Injury In Rats

C3-16 Lee, Stephanie 3:45 PM - 4:00 PM
University of Miami Miller School of Medicine
The Inflammasome Is Activated In The Cortex And Hippocampus Of Rats Following Penetrating Ballistic Brain Injury

C3-17 Ziebell, Jenna 3:00 PM - 3:15 PM
Barrow Neurological Inst. at Phoenix Children's Hospital
Distribution Of Microglial Morphologies Shift With The Blockade Of Nogo-66 Receptor

C3-18 Bedi, Supinder 3:15 PM - 3:30 PM
University of Texas, Health Science Center at Houston
Time Course Of Microglia/Macrophage Activation After Traumatic Brain Injury In Mice

C3-19 Johnson, Victoria 3:30 PM - 3:45 PM
University of Pennsylvania
SNTF Immunohistochemistry Identifies A Previously Undetected Population Of Degenerating Axons Following Traumatic Brain Injury

C3-20 Shields, Jessi 3:45 PM - 4:00 PM
Georgia Regents University
Toll-Like Receptor 4 Mediates Post-Traumatic Changes To The Circadian Clock

Poster Session C
3:00 - 4:00 pm

C3-21 Winston, Charisse 3:00 PM - 3:15 PM
Georgetown University
Apoe Influence On Dendritic Spine Levels Following Mild Traumatic Brain Injury

C3-22 Shapiro, Lee 3:15 PM - 3:30 PM
Texas A&M HSC
Altered Neurogenesis Following A Fluid Percussion Injury In Mice

C3-23 Yan, Hong 3:30 PM - 3:45 PM
University of Pittsburgh
Effect Of Traumatic Brain Injury On Wild-Type Alpha-Synuclein Expression In Rat Hippocampus

C3-24 Schneider, Brandy 3:45 PM - 4:00 PM
Wayne State University School of Medicine
Augmented Fear Behavior Following Traumatic Brain Injury Is Accompanied By Increased Cortical GABA

C3-25 Lifshitz, Jonathan 3:00 PM - 3:15 PM
Barrow Neurological Institute at Phoenix Children's Hospital
Astrocyte-Mediated Circuit Reorganization: Evidence From Synaptogenic Expression After Experimental Diffuse Traumatic Brain Injury

C3-26 Rumney, Benjamin 3:15 PM - 3:30 PM
University of Arizona
Morphological Reorganization Of Thalamic Neurons After Diffuse TBI May Underlie Attenuated Immediate Early Gene Activation

C3-27 Seidl, Stacey 3:30 PM - 3:45 PM
University of California, Davis
Stimulation Of The Medial Septum Drives Hippocampal Theta Oscillations Leading To Persistent Increases In Theta Phase Coherence

C3-28 Donovan, Virginia 3:45 PM - 4:00 PM
UC Riverside
Decreased Hemispheric Swelling Following TBI In Mice Lacking TREM2

C3-29 Rowe, Rachel 3:00 PM - 3:15 PM
Barrow Neurological Institute at Phoenix Children's Hospital
Experimental Diffuse Brain Injury Leads To Chronic Endocrine Dysfunction

C3-30 Kummer, Terrance 3:15 PM - 3:30 PM
Washington University School of Medicine
Axonal Injury In A Mouse Model Of Subarachnoid Hemorrhage

C3-31 Gomez-Pinilla, Fernando 3:30 PM - 3:45 PM
University of California Los Angeles
Gene Networks Analysis To Elucidate The Complexity Of TBI

C3-32 Lipinski, Marta 3:45 PM - 4:00 PM
University of Maryland, Baltimore
Disruption Of Autophagy After TBI Is Associated With Lysosomal Dysfunction And Neuronal Cell Death

Poster Session D
4:00 - 5:00 pm - Tuesday, July 1

TBI PROTECTION

D1-01 Godbout, Jonathan 4:00 PM - 4:15 PM
The Ohio State University
Methylene Blue Attenuates Traumatic Brain Injury Associated Neuroinflammation And Acute Depressive-Like Behavior In Mice

D1-02 Watts, Lora 4:15 PM - 4:30 PM
University of Texas Health Science Center San Antonio
Delayed Methylene Blue Improves Lesion Volume And Behavioral Outcome Following TBI.

D1-03 Gupta, Deepak 4:30 PM - 4:45 PM
AIIMS (All India Institute of Medical Sciences)
Hypothermia In TBI For Control of Intracranial Hypertension As Therapeutic Option: ICP Trends And Graded Hypothermia

D1-04 Wu, Ping 4:45 PM - 5:00 PM
University of Texas Medical Branch
Stem Cell Transplantation-Mediated Alteration of Microglial Phenotypes In Injured Mouse Brains

D1-05 Berman, Nancy 4:00 PM - 4:15 PM
Univ. Kansas Med. Ctr.
Changing The Outcome of Traumatic Brain Injury In Mice. No Genes. No Drugs.

D1-06 Hue, Christopher 4:15 PM - 4:30 PM
Columbia University
Dexamethasone Potentiates Recovery of The Blood-Brain Barrier After Primary Blast Injury In Vitro

D1-07 Yonutas, Heather 4:30 PM - 4:45 PM
University of Kentucky
Interactions Between Pioglitazone And Mitoneet Ameliorate Mitochondrial Dysfunction Following Traumatic Brain Injury

D1-08 Leung, Lai Yee 4:45 PM - 5:00 PM
Walter Reed Army Institute of Research
Effect of NNZ-2591 Treatment On Axonal And Synaptic Plasticity Following Penetrating Ballistic-Like Injury In Rats

D1-09 Shear, Deborah 4:00 PM - 4:15 PM
Walter Reed Army Institute of Research
Evaluation of Combined Administration of Dextrometho-rphan And Simvastatin In An Experimental Model of Traumatic Brain Injury

D1-10 Piao, Chunshu 4:15 PM - 4:30 PM
Ann & Robert H. Lurie Children's Hospital of Chicago Research Center
Thrombin Decreases Expression of GLAST And Inhibits Glutamate Uptake In Astrocytes Via The Rho Kinase Pathway

D1-11 Park, Eugene 4:30 PM - 4:45 PM
St. Michael's Hospital
Remote-Ischemic Preconditioning As A Prophylactic Method To Increase Biological Resilience To Mild Traumatic Brain Injury.

D1-12 Kumar, Raj 4:45 PM - 5:00 PM
University of Pittsburgh
Acute Interleukin-6 Trajectories After TBI: Relationship To Isolated Injury And Polytrauma And Associations With Outcome

D1-13 Cao, Yuli 4:00 PM - 4:15 PM
Karolinska Institute
Hypothermia And In Vitro High-Energy Trauma

D1-14 Kochanek, Patrick 4:15 PM - 4:30 PM
Safar Center for Resuscitation Research, Univ. of Pittsburgh
Multicenter Comparison of Five Therapies Reveals Therapeutic Potential For Levetiracetam: Operation Brain Trauma Therapy

D1-15 Cebak, John 4:30 PM - 4:45 PM
University of Kentucky
Protective Effects of Phenelzine Against Aldehyde-Induced Ex Vivo Oxidative Damage To Cortical Mitochondria

D1-16 Brockman, Erik 4:45 PM - 5:00 PM
University of Pittsburgh Medical Center
Polynitroxylated Pegylated Hemoglobin Improves Acute Physiology Vs. Blood After Traumatic Brain Injury Plus Hemorrhagic Shock

D1-17 Brabazon, Fiona 4:00 PM - 4:15 PM
USUHS
Intranasal Insulin Treatment of Traumatic Brain Injury

D1-18 Vemuganti, Raghu 4:15 PM - 4:30 PM
University of Wisconsin
ER Stress Inhibitor Salubrinal Is Neuroprotective After TBI

D1-19 Dixon, C. Edward 4:30 PM - 4:45 PM
University of Pittsburgh
Dose-Response Evaluation of Simvastatin In The Controlled Cortical Impact Model: Operation Brain Trauma Therapy Consortium

D1-20 Bergold, Peter 4:45 PM - 5:00 PM
State University of New York-Downstate Medical Center
Minocycline And N-Acetylcysteine Limit The Heteroge-neous Injury That Arises From A Single Closed Head Impact.

D1-21 Glushakov, Alexander 4:00 PM - 4:15 PM
University of Florida
Therapeutic Potential of The Prostaglandin E2 EP1 Receptor In Traumatic Brain Injury

D1-22 Browning, Megan 4:15 PM - 4:30 PM
Children's Hospital of Pittsburgh of UPMC
Benefits of Early Administration of Levetiracetam After Controlled Cortical Impact In Rats: Operation Brain Trauma Therapy

D1-23 Ferguson, Scott 4:30 PM - 4:45 PM
Roskamp Institute
Spatial Memory Normalization After Treatment With Anatabine Beginning 9 Months After Repetitive Mild TBI

Poster Session D

4:00 - 5:00 pm - Tuesday, July 1

D1-24 Harrison, Jordan 4:45 PM - 5:00 PM
Barrow Neurological Institute at Phoenix Children's Hospital
Acute Over-The-Counter Pharmacological Intervention Does Not Adversely Affect Behavioral Outcome Following Diffuse Traumatic Brain

D1-25 Harrison, Jordan 4:00 PM - 4:15 PM
Barrow Neurological Institute at Phoenix Children's Hospital
Remote Ischemic Conditioning As Pre-Hospital Therapeutic Intervention For Diffuse Traumatic Brain Injury

D1-26 Wu, Limin 4:15 PM - 4:30 PM
MGH
Neuregulin-1 Infusion After TBI In Adolescent Mice Improves Cognitive Performance During Adulthood

D1-27 Spurlock, Markus 4:30 PM - 4:45 PM
University of Miami
Multineurotrophin Expressing Fetal Cell Transplant In Penetrating Ballistic Brain Injury (Pbbi)

D1-28 Olson, Scott 4:45 PM - 5:00 PM
University of Texas Medical School at Houston
Sequential Beta-Blocker And Cellular Therapy For Traumatic Brain Injury

D1-29 Gomez-Pinilla, Fernando 4:00 PM - 4:15 PM
University of California Los Angeles
Activation of BDNF-Trkb Signaling Recruits Metabolic Signals To Improve Functional Recovery Following Brain Trauma

D1-30 Finan, John D. 4:15 PM - 4:30 PM
Columbia University
Intracerebroventricular Delivery of Chondroitinase ABC Reduces Post-Traumatic Brain Edema In Mice

D1-31 Hsieh, Christine 4:30 PM - 4:45 PM
San Francisco VA
CCR2 Deficiency Impairs Macrophage Infiltration And Improves Cognitive Function After Traumatic Brain Injury

D1-32 Symes, Aviva 4:45 PM - 5:00 PM
USUHS
Genetic Deletion of Parkin Enhances Recovery From TBI

D1-33 Gatson, Joshua 4:00 PM - 4:15 PM
UT Southwestern Medical Center
Chronic Administration of Resveratrol After Mild TBI Reduces Beta-Amyloid Plaque Load In The Brain of 5XFAD Mice

D1-34 Ji, Jing 4:15 PM - 4:30 PM
University of Pittsburgh
Micrornas Regulate Mitophagy After Traumatic Brain Injury

D1-35 Morganti, Josh 4:30 PM - 4:45 PM
University of California San Francisco
CX3CR1 Deficiency Ameliorates TBI-Induced Inflammatory Response And Cognitive Dysfunction

TBI MODELING

D2-01 Armstrong, Regina 4:00 PM - 4:15 PM
USUHS
Heterogeneous TBI Models Reveal Divergent Effects In Neuronal And Oligodendroglial Progenitors

D2-02 Wang, Ying 4:15 PM - 4:30 PM
Walter Reed Army Institute of Research
Characterization of Blast-Induced Vestibular Injury In Rats

D2-03 Effgen, Gwen 4:30 PM - 4:45 PM
Columbia University
Primary Blast Does Not Increase Vulnerability of Brain To Subsequent Primary Blast Or Glutamate Exposure

D2-04 Thorpe, Chevon 4:45 PM - 5:00 PM
Edward Via College of Osteopathic Medicine Cellular Mechanisms of Primary Blast- Induced Traumatic Brain Injury: Shock-Wave Neurotrauma

D2-05 Ruppert, Katherine 4:00 PM - 4:15 PM
University of Texas Medical Branch
Effects of Mild Blast-Induced Neurotrauma On Blood-Brain Barrier Permeability

D2-06 Avitua, Angela 4:15 PM - 4:30 PM
University of California, Davis
A New Rodent Model of Pediatric Sports-Related Concussion

D2-07 Wojnarowicz, Mark 4:30 PM - 4:45 PM
Boston university
Elucidating The Kinematics And Pathobiology of Blast-Related Traumatic Brain Injury And Sequelae In A Mouse Model

D2-08 Harper, Matthew 4:45 PM - 5:00 PM
VA Health Care System; University of Iowa
Blast-Induced TBI In Mice Elicits A Biphasic Decrement In The PERG That Correlates With Retinal Ganglion Cell Activity

D2-09 Tumer, Nihal 4:00 PM - 4:15 PM
University of Florida
Overpressure Blast Injury Induced Structural And Functional Changes In The Brain And Basilar Artery

D2-10 Povlishock, John 4:15 PM - 4:30 PM
Virginia Commonwealth University
Abstract Title Axonal Injury And Microglial Activation In Micropigs Following Diffuse Brain Injury: An OBTT Consortium Report.

D2-11 Sharrow, Keith 4:30 PM - 4:45 PM
Walter Reed Army Institute of Research
Characterization of A Blast-Induced Brain And Eye Injury Model In Rats

D2-12 Scultetus, Anke 4:45 PM - 5:00 PM
Naval Medical Research Center
A New Model of Traumatic Brain Injury (TBI) Simulating Penetrating Injuries Using A Captive Bolt In Swine

D2-13 Leung, Lai Yee 4:00 PM - 4:15 PM
Walter Reed Army Institute of Research Combined Hypoxemia & Hemorrhagic Shock Worsen Motor But Not Cognitive Function After Penetrating Ballistic-Like Brain Injury

D2-14 Leung, Lai Yee 4:15 PM - 4:30 PM
Walter Reed Army Institute of Research Penetrating Ballistic-Like Brain Injury Promotes Time-Dependent Cell Proliferation In Adult Rat Hippocampus

D2-15 Leung, Lai Yee 4:30 PM - 4:45 PM
Walter Reed Army Institute of Research Comprehensive Evaluation of Chronic Spatial Learning And Working Memory Deficits Following Closed-Head Concussive Injury In Rats

D2-16 Santamaria, Andrea 4:45 PM - 5:00 PM
University of Miami
Causes of Injury Variation In A Porcine Thoracic Contusion Model.

D2-17 Shear, Deborah 4:00 PM - 4:15 PM
Walter Reed Army Institute of Research
Longitudinal Profile of Sensorimotor Deficits Following Single And Repeated Projectile Concussive Injury (PCI)

D2-18 Yang, Zhihui 4:15 PM - 4:30 PM
University of Florida
Repetitive Mild Traumatic Brain Injury Mice Exhibit Structural And Histopathological Alterations And Long-Term Behavioral Changes

D2-19 McCabe, Joseph 4:30 PM - 4:45 PM
Uniformed Services Univeristy of the Health Sciences
Characterization of CCI Using High Speed Imaging

D2-20 McCutcheon, Victoria 4:45 PM - 5:00 PM
University of Toronto
Development And Validation of Two Zebrafish Models of TBI

D2-21 Mondello, Stefania 4:00 PM - 4:15 PM
University of Messina
Comparison of TBI Models Using Brain Damage Markers, And Histological And Behavioral Outcomes In Operation Brain Trauma Therapy

D2-22 Stemper, Brian 4:15 PM - 4:30 PM
Medical College of Wisconsin
Characterization of A Laboratory-Based Rodent Rotational Acceleration TBI Device

D2-23 Yu, Allen 4:30 PM - 4:45 PM
Duke University
In Vs. Out: Controversies In Shock Tube Blast Experiments

D2-24 Stemper, Brian 4:45 PM - 5:00 PM
Medical College of Wisconsin
Influence of Head Rotational Acceleration Pulse Shape On Brain Tissue Strains

Poster Session D

4:00 - 5:00 pm - Tuesday, July 1

D2-25 Tagge, Chad 4:00 PM - 4:15 PM
Boston University
Elucidating The Pathobiology of Impact Concussion In A Mouse Model of Mild Traumatic Brain Injury

D2-26 Bhatnagar, Tim 4:15 PM - 4:30 PM
University of British Columbia
Correlating Mechanical Strain And Biological Damage: An In Vivo, Rodent Model of Spinal Cord Injury

D2-27 McGuone, Declan 4:30 PM - 4:45 PM
Massachusetts General Hospital
Challenges In Assessing Tau In A Large Animal Model of TBI

D2-28 Sarvghad-Moghaddam, H. 4:45 PM - 5:00 PM
North Dakota State University
Computational Investigation of Brain Neurotrauma Biomechanics Under Blast

D2-29 Sarvghad-Moghaddam, H. 4:00 PM - 4:15 PM
North Dakota State University
Effect of Space Confinement On The Level of Blast Induced Traumatic Brain Injury

D2-30 Leonessa, Fabio 4:15 PM - 4:30 PM
Uniformed Services University of the Health Sciences
Limited Evidence of Brain Injury In Rats Exposed To Explosive-Driven Primary Blast

D2-31 Verley, Derek 4:30 PM - 4:45 PM
University of California Los Angeles
Role of The Contralesional Cortex In Forelimb Recovery After Experimental TBI

D2-32 Hernandez, Fidel 4:45 PM - 5:00 PM
Stanford University
Finite Element Simulation of Brain Deformation From Six Degree of Freedom Acceleration Measurements of Mild Traumatic Brain Injury

D2-33 Tucker, Laura 4:00 PM - 4:15 PM
Uniformed Services University of the Health Sciences
Anxiety-Like Behavior In Mice After Traumatic Brain Injury: Discussion And Comparison of Commonly-Used Tests And Measurements

D2-34 Ng, Kian Chye 4:15 PM - 4:30 PM
DSO National Laboratories
Metabolite, Histopathological And Functional Changes In The Hippocampus After Blast Exposure

D2-35 Pruitt, David 4:30 PM - 4:45 PM
The University of Texas at Dallas
Controlled-Cortical Impact Reduces Rats' Ability To Sustain Application of Submaximal Force

D2-36 Namjoshi, Dhananjay 4:45 PM - 5:00 PM
The University of British Columbia
Neuropathological And Biochemical Assessment of CHIMERA: A Novel Closed-Head Impact Model of Engineered Rotational Acceleration

D2-37 Cheng, Wai Hang 4:00 PM - 4:15 PM
University of British Columbia
Biomechanical And Functional Characterization of CHIMERA: A Novel Closed-Head Impact Model of Engineered Rotational Acceleration

D2-38 Mouzon, Benoit 4:15 PM - 4:30 PM
Roskamp Institute
Longitudinal Evaluation of Histological And Neurobehavioral Changes In A Mouse Model of R-Mtbi: A Follow Up At 2 Years Post Injury

Neurotrauma 2014 Agenda
Wednesday, July 2

Wednesday

7:00 am - 3:00 pm	Neurotrauma Registration Desk Open	Yerba Buena Foyer
7:00 am - 7:45 am	Continental Breakfast / Visit Exhibits / Open Poster Viewing [0.75 CME]	Yerba Buena 7/8
7:50 am - 8:00 am	President's Welcome - Jacqueline Bresahan PhD, UCSF	Yerba Buena 9
8:00 am - 10:00 am	**Optimizing Rehabilitation Strategies in Neurotrauma** [2.00 CME] Sponsored by CRAIG H. NEILSEN FOUNDATION	Yerba Buena 9
	Chair: Michael Beattie, PhD; University of California San Francisco	
8:00-8:40	Harnessing Activity to Promote Corticospinal Tract Axonal Outgrowth and Motor Function After Injury John Martin, PhD; Columbia University	
8:40-9:20	Cellular and Molecular Regulators of Recovery After SCI D. Michele Basso, PhD; Ohio State University	
9:20-10:00	Neuroplasticity and Repair in the CNS Daniel Lu, PhD; University of California Los Angeles	
10:00 am - 10:30 am	**NNS Awards Ceremony / iPad Drawing**	Yerba Buena 9
10:30 am - 11:00 am	Coffee Break	Yerba Buena 7/8 Foyer
11:00 am - 12:00 pm	**Novel Understandings and Approaches for the Future** [1.00 CME] Chair: Adam Ferguson, PhD; University of California San Francisco	Yerba Buena 9
11:00-11:30	Applications of TDA (Topological Data Analysis) to Brain Science Pek Lum, MD; Ayasdi Inc.	
11:30-12:00	The Glymphatic System - Potential Roles in Traumatic Brain Injury Maiken Nedergaard, PhD; University of Rochester	
12:00 pm - 1:30 pm	FREE TIME - LUNCH ON YOUR OWN	
12:00 pm -1:30 pm	**WiNTR Lunch Workshops** [1.50 CME] [Ticket Required] Sponsored by CRAIG H. NEILSEN FOUNDATION	Yerba Buena 1-6
	Obtaining Funding Information and Resources in Times of Austerity Linda Noble , PhD & Jonathan Lifshitz, PhD	Yerba Buena 1
	Communicating Effectively in Written, Oral, Visual & Digital Modes Diane Snow, PhD & David Magnuson, PhD	Yerba Buena 2
	Publishing Negative Results: When, Where, Why and How? Amy Wagner, PhD & Courtney Robertson, PhD	Yerba Buena 3
	The Digital Laboratory: Becoming "Tech Savvy" in Your Research Program Adam Ferguson, PhD & D. Michele Basso, PhD	Yerba Buena 4
	Research Design for Young Investigators Michelle LaPlaca, PhD & Theresa Currier-Thomas, PhD	Yerba Buena 5
	Current Hot Topics of Interest (Open Discussion) Kathryn Saatman, PhD & John Povlishock, PhD	Yerba Buena 6
1:30 pm - 2:30 pm	**Chronic Pain and CNS Injury** [1.00 CME] Sponsored by Mission Connect a project of TIRR Foundation	Yerba Buena 9
	Chair: Claire Hulsebosch, PhD; University of Texas Medical Branch	
1:30-2:00	Functional and Neurobiological Consequences of Opioid Administration in a Rodent Model of SCI Michelle Hook, PhD; Texas A&M University	
2:00-2:30	Transplant-Mediated Repair of Spinal Cord GABAergic Inhibitory Circuitry to Treat the "Disease" of Neuropathic Pain Allan Basbaum, PhD; University of California San Francisco	

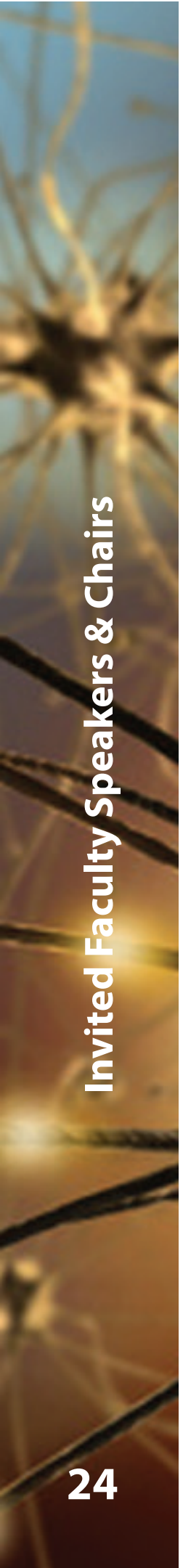
Neurotrauma 2014 Agenda
Wednesday, July 2

2:30 pm - 4:00 pm	**Translational Concepts in Cognitive Rehabilitation** [1.50 CME] Chair: Amy Wagner, PhD; University of Pittsburgh	Yerba Buena 1-6
2:30-3:00	Cognitive Constructs in Rodents: A Roadmap for Assessing Cognitive Dysfunction and Recovery after TBI Edda Thiels, PhD; University of Pittsburgh	
3:00-3:30	CCI Model As An Exemplar To Study Implicit & Explicit Learning & Memory Networks & Develop An Experimental Cognitive Rehab Model Amy Wagner, PhD; University of Pittsburgh	
3:30-4:00	Clinical Approaches to Cognitive Training in NeuroRehabilitation: Translating the Bench to the Bedside and Back Again Elizabeth Skidmore, PhD; University of Pittsburgh	
2:30 pm - 4:00 pm	**Sensory Disorders After Military Brain Injury** [1.50 CME] Chair: Frederick Gallun, PhD; Portland VA Medical Center	Yerba Buena 9
2:30-3:00	Sensory and Communication Disorders in TBI and Polytrauma Henry Lew, MD, PhD; University of Hawaii, VCU, DVBIC	
3:00-3:30	Functional Measures of Hearing Performance in Blast-Exposed Military Personnel Douglas Brungart, PhD; Walter Reed National Military Medical Center	
3:30-4:00	Central Auditory Processing Following Blast Exposure in a Veteran Population: Behavioral and Electrophysiological Evidence Frederick Gallun, PhD; Portland VA Medical Center	
2:30 pm - 4:00 pm	**SCI and TBI Model Selection** (Roundtable) [1.50 CME] Chair: Stephen Scheff, PhD; University of Kentucky	Yerba Buena 10-15
2:30-3:00	History and Description of Current Models Used in Experimental TBI Stephen Scheff, PhD; University of Kentucky	
3:00-3:30	Spinal Cord Injury Models and Trials: The Fascination of What's Difficult Andrew Blight, PhD; Acorda Therapeutics	
3:30-4:00	The Use of Animals Models in SCI for Rationalizing Clinical Translation: Pros and Cons Brian Kwon, PhD; University of British Columbia	
4:00 pm - 4:15 pm	**Closing Remarks & Introduction of 2015 President**	Yerba Buena 9
4:30 pm - 5:30 pm	NNS 2015 Planning Committee Meeting	Nob Hill D

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 2014 is Dr. Patricia Washington from Georgetown University. In addition to attending the upcoming 32nd Annual NNS Symposium in San Francisco, Dr. Washington will participate in on-site collaborative research at the Southern General Hospital in Glasgow, UK, in the neurotrauma research laboratory of Dr. William Steward.

The award will be officially recognized during the NNS Awards Ceremony on Wednesday July 2nd. Please join us to congratulate Dr. Washington on her achievement!



Invited Faculty Speakers & Chairs

NAME		DEGREE	UNIVERSITY/ COMPANY	DAY	ROLE
Vicki	Anderson	PhD	Murdoch Children's Research Institute	TUES	Speaker
Kim	Anderson-Erisman	PhD	University of Miami	MON	Chair
Coleen	Atkins	PhD	University of Miami	TUES	Speaker/Chair
Neeraj	Badjatia	MD	University of Maryland	MON	Speaker
William	Barsan	PhD	University of Michigan	MON	Speaker
Allan	Basbaum	PhD	University of California San Francisco	WED	Speaker
D. Michele	Basso	PhD	Ohio State University	WED	Speaker
Hülya	Bayir	PhD	Safar Center for Resuscitation Research	TUES	Speaker
Michael	Beattie	PhD	University of California San Francisco	WED	Chair
Mitchel	Berger	MD	University of California San Francisco	MON	Speaker
Andrew	Blight	PhD	Acorda Therapeutics, Inc.	WED	Speaker
Jacqueline	Bresnahan	PhD	University of California San Francisco	MON	Program Chair
Douglas	Brungart	PhD	Walter Reed NMMC	WED	Speaker
Glenn	Cockerham	MD	Stanford University	SUN	AANS Speaker
Kenneth	Curley	MD	US Army	TUES	Speaker
Steven	DeKosky	MD	University of Virginia	MON	Speaker
Ramon	Diaz-Arrastia	MD, PhD	UnSUHS	SUN	AANS Speaker
Adam	Ferguson	PhD	University of California San Francisco	WED	Chair
Candace	Floyd	PhD	University of Alabama	WED	Abstract Chair
Frederick	Gallun	PhD	Portland VA Medical Center	WED	Speaker
Karunesh	Ganguly	PhD	University of California San Francisco	TUES	Speaker
David	Gater	PhD	Penn State Hershey Medical Center	MON	Speaker
Guido	Gerig	PhD	University of Utah	TUES	Speaker
Christopher	Giza	MD	University of California Los Angeles	MON	Speaker/Chair
Grace	Griesbach	PhD	Centre for Neuroskills	TUES	Speaker
James	Guest	MD, PhD	University of Miami	MON	Speaker
Scott	Hamilton		Circumventure Learning Corp.	SUN	Keynote Speaker
Gerri	Hanten	PhD	Baylor College of Medicine	TUES	Speaker
Susan	Harkema	PhD	University of Louisville	SUN	Speaker
Gregory	Hawryluk	PhD	University of California San Francisco	SUN	AANS Speaker
Ron	Hayes	PhD	Banyan Biomarkers, Inc.	TUES	Speaker
Caitlin	Hill	PhD	Burke-Cornell Medical Research Institute	TUES	Chair
Gregory	Holmes	PhD	Penn State University College of Medicine	MON	Speaker/Chair
Michelle	Hook	PhD	Texas A&M University	WED	Speaker
Claire	Hulsebosch	PhD	University of Texas Medical Branch	WED	Chair
Andrei	Irimia	PhD	University of Southern California	TUES	Speaker
Ranu	Jung	PhD	Florida International University	TUES	Speaker
Anthony	Kline	PhD	University of Pittsburgh	TUES	Speaker
Zhifeng	Kou	PhD	Wayne State University	MON	Chair
Joel	Kramer	PhD	University of California San Francisco	TUES	Speaker
Brian	Kwon	PhD	University of British Columbia	WED	Speaker
Michelle C.	LaPlaca	PhD	Georgia Tech/Emory	TUES	Chair
Peter	LeRoux	MD	Mainline Health System	SUN	AANS Speaker
Allan	Levi	MD, PhD	University of Miami	SUN	AANS Speaker
Harvey	Levin	PhD	Baylor College of Medicine	TUES	Chair
Henry	Lew	MD, PhD	University of Hawaii and VCU	WED	Speaker
Jonathan	Lifshitz	PhD	University of Arizona	TUES	Speaker
Daniel	Lu	PhD	University of California Los Angeles	WED	Speaker
Pek	Lum	MD	Ayasdi Inc.	WED	Speaker

Invited Faculty Speakers & Chairs

NAME		DEGREE	UNIVERSITY/ COMPANY	DAY	ROLE
David	Magnuson	PhD	University of Louisville	MON	Chair
Geoff	Manley	MD, PhD	University of California San Francisco	MON	Speaker
Martin	Marsala	MD	University of California San Diego	SUN	AANS Speaker
John	Martin	PhD	City University of New York	WED	Speaker
Tricia	Merkley	PhD	Baylor College of Medicine	MON	Speaker
Lee	Miller	MD	Northwestern University	SUN	AANS Speaker
Bruce L.	Miller	MD	University of California San Francisco	MON	Speaker
Maiken	Nedergaard	PhD	University of Rochester	WED	Speaker
Linda	Noble-Haeusslein	PhD	University of California San Francisco	TUES	Speaker
Kevin	Pearce		Kevin Pearce Foundation/Love Your Brain	MON	Keynote Speaker
Christian	Poellabauer	PhD	University of Notre Dame	SUN	AANS Speaker
John	Povlishock	PhD	Virginia Commonwealth University	TUES	Chair
Mayumi	Prins	PhD	University of California Los Angeles	TUES	Speaker/Chair
Roman	Reed		Roman Reed Foundation	SUN	Keynote Speaker
Courtney	Robertson	MD	Johns Hopkins University	MON	Speaker
Susanna	Rosi	PhD	University of California San Francisco	TUES	Speaker/Chair
Kathryn	Saatman	PhD	University of Kentucky	TUES	Chair
Uzma	Samadani	MD, PhD	NYU Medical Center	SUN	AANS Speaker
Stephen	Scheff	PhD	University of Kentucky	WED	Speaker/Chair
Martin	Schubert	PhD	University of Zürich	MON	Speaker
Jerry	Silver	MD	Case Western Reserve Univ	MON	Speaker
Elizabeth	Skidmore	PhD	University of Pittsburgh	WED	Speaker
Diane	Snow	PhD	University of Kentucky	WED	Chair
Michael	Sofroniew	PhD	University of California Los Angeles	TUES	Speaker
John	Steeves	PhD	University of British Columbia	MON	Speaker
Keith	Tansey	MD, PhD	Emory University	TUES	Chair
Edda	Thiels	PhD	University of Pittsburgh	WED	Speaker
Theresa C.	Thomas	PhD	University of Arizona	MON	Chair
Hilaire	Thompson	PhD	University of Washington	TUES	Speaker
Mark	Tuszynski	PhD	University of California San Diego	MON	Speaker
John	Van Horn	PhD	University of Southern California	TUES	Chair
Amy	Wagner	PhD	University of Pittsburgh	WED	Speaker/Chair
Michael	Whalen	PhD	Harvard University	TUES	Speaker
Jefferson	Wilson	MD, PhD	Toronto University Hospital	SUN	AANS Speaker
Edward	Wirth	MD, PhD	Asterias Biotherapeutics, Inc.	MON	Speaker
Matthew	Wright	PhD	University of California Los Angeles	TUES	Speaker
Chengyuan	Wu	MD	Thomas Jefferson University	SUN	AANS Speaker
Xiao-Ming	Xu	PhD	Indiana University School of Medicine	MON	Speaker
Ross	Zafonte	DO	Massachusetts General Hospital	SUN	AANS Speaker

Neurotrauma 2014
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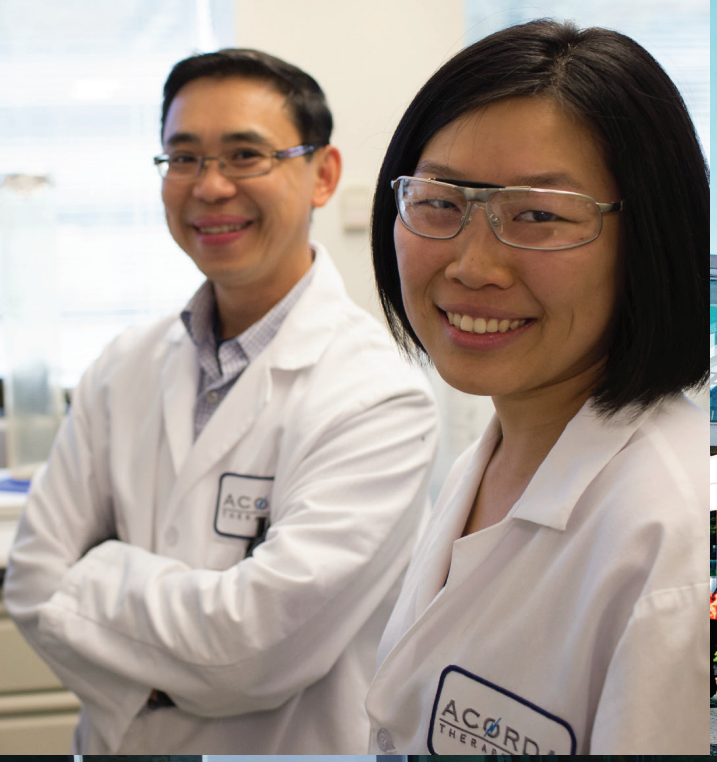

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DOI: 10.1089/neu.2014.9935.abstracts

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T1-01

REPEAT MILD TRAUMATIC BRAIN INJURY IN ADOLESCENT RATS ACCELERATES ALZHEIMER'S DISEASE PATHOGENESIS

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Traumatic brain injury (TBI) is a risk factor for Alzheimer's disease (AD), but the cumulative effects of mild repeat TBI (RTBI) in the adolescent brain on AD pathogenesis are unknown. We hypothesized that RTBI would increase secretase concentration acutely in the wild-type Sprague-Dawley rats and accelerate the accumulation of amyloid beta (Aβ) chronically in amyloid precursor protein/presenilin 1 transgenic rats (APP/PS1). Postnatal day 35 (P35) male wild-type rats received sham or 4 RTBI at 24 hour intervals ($4RTBI_{24}$) using a closed-head injury model. Bilateral cortices were analyzed 24 or 48 hours post-injury using western blots to measure the concentration of beta-site-APP-cleaving-enzyme-1 (BACE1) and PS1, two secretases required for Aβ production. The P35 APP/PS1 rats received sham, $4RTBI_{24}$ or 4 RTBI at 72 hour intervals ($4RTBI_{72}$) and were perfused at 12 months of age. One-way ANOVA with Tukey-Kramer post-hoc was used to compare optical densities of BACE1, PS1, and total Aβ deposits (including puncta, clusters, and plaques) between injury groups. In wild-types, $4RTBI_{24}$ increased 24 hour BACE1 levels in ipsilateral cortex 35% greater than sham ($p=0.02$), but returned to sham levels by 48 hours. $4RTBI_{24}$ did not affect PS1 levels in wild-type rats at either time point. In APP/PS1 rats, $4RTBI_{24}$ had significantly more Aβ deposits in the ipsilateral hippocampus relative to the sham ($p=0.040$) and $4RTBI4_{72}$ ($p=0.046$) groups, which did not differ from each other. There was no difference between ipsilateral and contralateral hippocampi. These findings demonstrate that repeat injuries in adolescence may accelerate subsequent Aβ deposition. Since BACE1 increased transiently, its relationship with chronic Aβ remains uncertain. Interestingly, when injury levels were increased to allow metabolic recovery between impacts, chronic Aβ deposition is similar to that seen after sham. This study emphasizes the need for compliance in return-to-play guidelines to minimize the risk for accelerated Aβ accumulation among those pre-disposed to AD.

Supported by UCLA BIRC, KO8AG34628, NS058489-01

Key words
Alzheimer's disease, developmental, mild TBI

T1-02

THE DEVELOPMENT OF EPILEPTOGENIC ACTIVITY AFTER DIFFUSE BRAIN INJURY IN SWINE

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The potential mechanisms of epileptogenesis after diffuse brain injury were studied using a model of closed-head rotational acceleration in swine. We performed in vivo extracellular recordings in order to investigate changes in hippocampal function post injury. We compared baseline oscillatory activity and responses to stimulation in sham, single, and repetitively injured animals.

Male Yucatan swine (6m) underwent coronal rotational acceleration (180–260 rad/sec) with little or no loss of consciousness and minimal subdural bleeding. We recorded changes in the synaptic inputs post stimulation with 32-channel probes and correlated the results to our previous in vitro hippocampal slice recordings 7 days post injury. Paired-pulse paradigms were utilized in order to examine changes in excitability and neurotransmitter release, while theta burst stimulation was induced to provoke epileptiform activity.

Hippocampal recordings were analyzed for epileptiform activity, synaptic facilitation, and changes in excitability after theta burst stimulation. Stimulation was performed in the Schaffer collaterals and the entorhinal cortex while recording from all layers of the dorsal hippocampus. Traces recorded in CA1 in response to single and paired stimulations had significantly altered waveforms. Paired pulse facilitation in CA1 was altered at 7 d post injury, potentially due to changes in neurotransmitter release probability. There were also significant changes in responses to single pulse stimulation after theta burst stimulation, as well as altered baseline activity (sharp waves and paroxysmal depolarizing shifts) compared to sham. Responses to stimulation in animal injured twice (2X180 rad/sec, 7 days apart) produced long-lasting depolarization compared to a single injury. These alterations suggest an increased post-synaptic excitability or a shift in the excitation-inhibition balance of the local circuitry.

These data suggest that diffuse brain injury may induce hippocampal axonal and synaptic dysfunction, and changes in hippocampal cellular excitability. Over time post injury these changes may lead to circuit-level changes in the hippocampus that will elicit sub-clinical epileptiform activity and potentially lower seizure thresholds.

Support: CURE Taking Flight, VA RRD Merit

Key words
circuitry, electrophysiology, excitability, hippocampus, in vivo, mild traumatic brain injury (mTBI)

T1-03

AUDITORY SELECTIVE ATTENTION IMPAIRMENTS IN BLAST-EXPOSED VETERANS WITH TRAUMATIC BRAIN INJURY

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A common complaint among returning combat veterans who have experienced some form of blast-related traumatic brain injury (bTBI)

is difficulty understanding speech in noisy environments. Given that many veterans have noise-induced hearing deficits, hearing loss is one factor that may contribute to such complaints. Specifically, sensorineural hearing loss likely interacts with damage to cortical structures important for controlling selective attention, leading to severe difficulties when trying to communicate in everyday social settings. We evaluated 10 bTBI veterans' hearing status as well as their performance on a selective auditory attention task. In the veterans tested, audiograms revealed near normal auditory thresholds (within 20 dB of normal limits). In addition, a more sensitive test of supra-threshold temporal coding fidelity in the brainstem recently developed in our laboratory revealed responses within the normal range for healthy young adults. Thus, in this pilot study, there was no evidence for sensorineural hearing deficits, even using new methods for revealing differences in supra-threshold hearing. The bTBI veterans performed a selective auditory attention task in which they were instructed to categorize the pitch contour of one of three simultaneously occurring melodies presented from three differently perceived locations (either rising, falling, or alternating). Such a task not only requires fine attentional control, but also temporally precise neural representations of the incoming sensory information. Performance was significantly worse compared to 17 normal-hearing, non-TBI controls. EEG-recorded evoked response potentials to correctly identified trials showed that in those veterans who could perform the task at above-chance levels, attention modulated the neural representation of the auditory input weakly or not at all, whereas healthy controls consistently show such modulation. Although these results do not rule out auditory sensory deficits as a contributing factor to selective auditory attention deficits in the general population of bTBI veterans, they suggest that blast exposure damage affects cortical regions responsible for controlling selective auditory attention. These findings are a step toward developing early pre-clinical diagnostic markers for long-term neurobehavioral disorders commonly associated with bTBI.

Key words
audiotory selective attention, behavioral, blast injury, EEG, veterans

T1-04

CCR2 ANTAGONISM ALTERS BRAIN MACROPHAGE POLARIZATION AND AMELIORATES COGNITIVE DYSFUNCTION INDUCED BY TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) initiates a robust innate immune response, which has been shown to persist for years following the initial event, and ultimately affects cognitive function. In patients who survive TBI, there are increased levels of the chemokine CCL2 in the cerebrospinal fluid (CSF), suggesting involvement of CCL2-CCR2 signaling axis following trauma. However, it is unclear what role $CCR2^+$ macrophages play in TBI-induced sequelae. Herein we used the unique $CX3CR1^{GFP/+}CCR2^{RFP/+}$ reporter mice, to define the temporal kinetics of TBI-induced CCR2 macrophage accumulation in the brain spanning acute (3–6 hrs), subacute (12–48 hrs) and chronic (7–28 d) time points. We found that accumulation of $CCR2^+$ macrophages is temporally restricted following to 12–24 hrs post injury. Interestingly, a significant number of CCR2+ cells began to express CX3CR1 simultaneously, which persisted through 7 days post injury. Gene expression analyses of multiple macrophage polarization markers revealed distinct temporal expression spanning the M1/M2 activation continuum across all time points. Moreover, multivariate analysis revealed distinct relationships between three macrophage subsets and their inflammatory gene expression profile. Combined, these findings identified a therapeutic window for targeting $CCR2^+$ macrophage accumulation following TBI. In wildtype mice, treatment with a novel phase-1 CCR2 antagonist, reduced accumulation of peripheral macrophages, disrupted neurotoxic macrophage polarization and prevented increased NADPH oxidase gene expression one day post-injury. Cumulatively, this treatment strategy prevented TBI-induced hippocampal learning and memory deficits 28 days post-injury. These data suggest that the accumulation of $CCR2^+$ macrophages contributes to TBI-induced cognitive decline and that pharmacologic agents can reverse this cognitive decline, which supports early intervention in patients with TBI.

Funding
This work was supported by the NIH R01 CA133216 (S.R.), R21 AG042016 (S.R.), Alzheimer Association IIRG-11-202064 (S.R.).

Key words
antagonist, CCR2, hippocampus, macrophage, multivariate analysis

T1-05

INFLAMMATION IN THE PAIN PATHWAY IN A MODEL OF MILD CLOSED HEAD INJURY: IMPLICATIONS FOR POST-CONCUSSION HEADACHE

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Headache is a hallmark symptom of concussion. Post-concussion headache (PCH) can be a new headache resulting from concussion or worsening of a pre-existing headache disorder. In many patients, it resolves in three months; in others, it persists for much longer. Understanding the post-concussion symptomology including headache is important for concussion management. The goal of this study was to compare changes in the trigeminal pain pathway and related behavior between a mild CCI injury (with focal-diffuse features) and a mild closed head injury (CHI) injury (with diffuse injury only). Male Sprague Dawley rats were randomized into CCI, single CHI, or repetitive (2-hit) CHI and compared to control groups. Baseline and weekly post-injury testing included von Frey (mechanical) sensory testing for the presence of allodynia, rotarod for balance, and Barnes maze for detecting deficits in spatial learning and memory. Changes in markers of injury/inflammation including beta amyloid precursor protein (β-APP), glial fibrillary acidic protein (GFAP), Iba-1 microglial, and inducible nitric oxide synthase (iNOS) were determined in the trigeminal pain pathway using immunohistochemistry, western blot, or qRT-PCR. Changes in the nociceptive neuropeptide, calcitonin gene-related peptide (CGRP) were also compared between injuries. Periorbital allodynia along with motor and learning deficits were dependent on the type of injury and number of injuries ($p < 0.01$). Group differences were found in the location and grading of β-APP accumulation, astrogliosis and microglial activation. Graded increases in CGRP and iNOS levels were found in the trigeminal pathway in CCI and CHI groups, $p < 0.001$. In conclusion, the type of injury (primarily focal or diffuse) and number of injuries influence the degree and distribution of inflammation, and nociceptive responses. Peripheral and central sensitization are evidenced by the presence of mechanical allodynia, inflammation, and alterations in trigeminal pain pathway. Findings indicate the importance of post-concussion

inflammation in headache chronification with implications for the management of post-concussion syndrome.

Key words
closed head injury, concussion, headache, post-concussion syndrome, post-traumatic headache

T1-06

ADVANCED BIOMATERIAL STRATEGIES FOR MICRO-TISSUE ENGINEERED NEURAL NETWORKS TO RESTORE BRAIN CIRCUITS

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Disruption of the connectome is a prominent feature of many neurological diseases and trauma. There is currently no strategy to repair long-distance axonal connections in the brain; therefore, we have developed micro-tissue engineering techniques to generate neurons with long axonal tracts encased in miniature hydrogel tubes as a strategy to restore long-distance axonal connections and neural populations. We previously found that these preformed micro-tissue engineered neural networks (TENNs) may be drawn into a needle and stereotaxically delivered into the rodent brain to reconstruct lost cortico-thalamic pathways, with evidence of transplant neuronal survival, maintenance of axonal architected, and synaptic integration into the cortex. Here, we have advanced the biomaterial encasement strategy to allow for needle-less delivery of preformed micro-TENNs to minimize insertion trauma. The micro-TENNs were composed of a small hollow hydrogel shell (≤ 700 μm OD) with an extracellular matrix interior (350 μm ID). These micro-TENNs consisted of agarose coated with low viscosity carboxymethylcellulose (CMC). Upon mild dehydration, coated micro-TENNs were able to withstand a force of $0.89 +/- 0.45$ N before buckling, whereas a solid agarose cylinder of the same size only withstood a force of less than 10 μN, thus the CMC coating increased the stiffness by five orders of magnitude. The needle to insert control (uncoated) micro-TENNs was almost 1/6 bigger than the needle-less (coated) micro-TENN; therefore, we anticipate that the needle-less method will minimize insertion damage due to a reduced form factor. We are currently evaluating host responses and micro-TENN neuronal survival and integration using needle versus needle-less delivery. Our novel micro-TENNs are the first strategy capable of facilitating nervous system repair by simultaneously providing neuronal replacement and re-creating long-distance axon pathways in the brain. The micro-TENN approach offers a new ability to treat several disorders that disrupt the connectome, including Parkinson's disease, TBI, stroke, Gulf War Illness, and brain tumor excision.

Key words
axonal tracts, biomaterials, cell replacement, tissue engineering

T1-07

INCREASED CSF NLRP3 BUT NOT NLRP1 AFTER SEVERE TRAUMATIC BRAIN INJURY IN CHILDREN

Simon, D.W.[1,2], Wallisch, J.[1], Bell, M.J.[1,2], Bayir, H.[1–3], Aneja, R.K.[1,2], Janesko-Feldman, K.[2], Kochanek, P.M.[1,2], Clark, R.S.[1,2]
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The NOD-like receptor, pyrin domain containing (NLRP) 1 and 3 inflammasomes are implicated in inflammation and secondary injury following traumatic brain injury (TBI). NLRPs recruit pro-caspase-1 and pro-interleukin-1β into the inflammasome, resulting in activation of caspase-1 and formation of interleukin-1β, both shown to be increased in cerebrospinal fluid (CSF) of children following severe TBI. NLRP1 is classically recognized for activation by *Bacillus anthracis* toxin, whereas in addition to microbial pathogens, NLRP3 is activated by oxidative stress and β-amyloid. We sought to determine whether one or both of the inflammasome proteins NLRP1 and NLRP3 were detectable in CSF of pediatric patients following severe TBI. CSF was obtained from children ($n=18$) treated with CSF diversion via an external ventricular drain after severe TBI in this IRB approved study. Lumbar CSF from children without TBI or meningitis served as controls ($n=8$). CSF levels of NLRP1 and NLRP3 were determined at four time intervals (0–24 h, 45–48 h, 49–72 h, and >72 h after injury) using enzyme-linked immunosorbent assay. CSF NLRP1 levels were below level of detection (<18.75pg/mL) in control subjects and were detected in only 2/18 TBI patients and only at a single time point (<24 h). In contrast, CSF NLRP3 levels were increased vs. controls across points (control $=0.36\pm0.04$, 0–24 h $=14.13\pm2.90$, 25–48 h $=4.08\pm1.01$, 49–72 h $=5.80\pm1.67$, >72 h $=8.48\pm1.92$ ng/mL; mean $\pm$ SEM; $p<0.001$). However, CSF NLRP3 levels did not correlate with age, sex, mechanism of injury, or outcome by univariate analysis. In conclusion, NLRP3, but not NLRP1, was increased in CSF of pediatric patients following severe TBI. To our knowledge, this represents the first study evaluating specific NLRPs after pediatric TBI and suggests prominent NLRP3 inflammasome formation, perhaps triggered by oxidative stress and/or β-amyloid, after TBI. Support: T32HD40686

Key words
inflammasome, NLRP3, traumatic brain injury

T1-08

THE POST TRAUMATIC BRAIN INJURY INFLAMMASOME AND RESPONSE TO AUTOLOGOUS CELL THERAPY

Liao, G.P., Hetz, R.A., Jimenez, F., Chang, J.T., Moore, A.N., Kosmach, S.C., Day, M., Lee, D.A., Worth, L.L., Savitz, S.I., Dash, P., Cox, C.S.
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Traumatic brain injury (TBI) elicits a complex neurologic and systemic inflammatory response. Cell therapy may have potential advantages over single agents as cellular bioreactors sense and respond to numerous environmental signals. However, interpreting the inflammasome response using biomarker data in clinical trials is challenging. This study evaluates the ability of bioinformatic techniques to evaluate cell therapy effects to relevant biomarkers during neurointensive care.

Interval plasma samples from 24–96 hours post TBI were obtained from three groups (TBI alone (n = 3), TBI + 6 million cells/kg (n = 4), TBI + 9 million cells/kg (n = 5)) in the prospective Phase II Adult Bone Marrow Derived Mononuclear Cell Therapy for TBI clinical trial. The cell therapy groups were treated intravenously within 48 hours of injury. A multiplex magnetic bead-based assay was used to

quantify select pro- (IL-1ß, IL-6, IFN-γ, TNF-α) and anti- (IL-4, IL-10) inflammatory cytokines. After normalizing each cytokine to baseline levels per patient, hierarchical clustering was used to generate dendrogram heat maps using Pearson correlated row distance measures and pairwise average-linkage clustering. Each cytokine dendrogram heat map was examined to determine if rows (patients) stratified according to treatment group.

Hierarchal clustering and dendrogram heat map generation identified IL-1β, IL-4 and TNF-α as cytokines where the dendrogram pattern correlated with the assigned treatment groups. The dendrogram clustering also demonstrated a treatment dose dependent reduction for the pro-inflammatory cytokines (IL-1β and TNF-α) and increase for the anti-inflammatory cytokine (IL-4) levels from 24–96 hours.

Our study suggests that hierarchical clustering and dendrogram heat mapping may be used to identify plasma cytokines associated with the treatment effect of cell therapy. The treatment effect of intravenous autologous bone marrow mononuclear cells for TBI in the acute setting appears to be most associated with the reduction of pro-inflammatory IL-1β and TNF-α levels and increase of anti-inflammatory IL-4 levels.

Key words
biomarker, cell therapy, clincal trial, inflammasome, inflammation

T1-09

INVERSE NEUROVASCULAR COUPLING TO CORTICAL SPREADING DEPOLARIZATIONS IN SEVERE BRAIN TRAUMA

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Cortical spreading depolarization (CSD) causes breakdown of electrochemical gradients following TBI, but also elicits dynamic changes in regional cerebral blood flow (rCBF) that range from physiologic neurovascular coupling (hyperemia) to pathological inverse coupling (hypoperfusion). The purpose of this study was to determine whether pathological inverse neurovascular coupling occurs as a mechanism of secondary injury. In 24 TBI patients requiring craniotomy, CSDs were monitored with subdural electrode strips and rCBF was measured with a parenchymal thermal diffusion probe. The status of cerebrovascular autoregulation was monitored as a correlation between blood pressure and rCBF. The rCBF response to CSD was obtained for 196 events in 5 patients. In one patient with intact cerebrovascular autoregulation, CSD induced only hyperemic responses (794% increase), while another patient with impaired autoregulation exhibited only the inverse (hypoperfusion) response (-24% decrease). By contrast, three patients exhibited dynamic changes in neurovascular coupling to CSDs through the course of monitoring. One exhibited increasing severity of the pathological inverse response (-14%, -29%, -79% decrease, $p<0.05$) that coincided with progressive worsening of cerebrovascular autoregulation (Pearson coefficient 0.04, 0.14, 0.28, $p<0.05$). Another exhibited a transformation from physiological hyperemic coupling (44% increase) to pathological inverse coupling (-30% decrease) ($p<0.05$) that coincided with a loss of autoregulation (Pearson coefficient $0.19\rightarrow0.32$, $p<0.05$). Pathologic inverse coupling was only observed with electrodes placed in or adjacent to evolving lesions. Patients with good 6-month outcomes had higher perfusion (46.8 ± 6.5 ml/100 g/min) than patients with poor outcomes (32.3 ± 3.7 ml/100 g/min) ($p<0.05$). These results establish inverse neurovascular coupling to CSD as a novel mechanism of secondary injury in TBI and suggest that CSD, the neurovascular response, cerebrovascular autoregulation, and ischemia are critical processes to monitor and target therapeutically in the management of brain injury.

Key words
cortical spreading depolarization, ischemia, neurovascular coupling, regional cerebral blood flow

T1-10

GENETICALLY-MODIFIED NEURAL PROGENITOR CELL TRANSPLANTATION FOR THE TREATMENT OF TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) represents a serious public health problem as there are no clinically-available treatments to mitigate the functional consequences experienced by patients. Neural progenitor cells (NPCs) hold significant promise as a potential treatment strategy for TBI due to the numerous intrinsic advantages of the cells, including the secretion of neurotrophic factors. Neurotrophins are critical for neuronal repair and survival, but their clinical use after injury is limited by differential binding specificities, short half-lives, and complicated delivery issues. We hypothesized that pericontusional transplantation of NPCs that were genetically modified to secrete a synthetic, human multineurotrophin (MNTS1) would overcome some of the limitations of traditional neurotrophin therapy. MNTS1 is a multifunctional, multitargeting neurotrophin that recapitulates the combined biological activity of three neurotrophins and induces the prosurvival signaling activity of all three tropomyosin-related kinase (Trk) receptors. NPCs were obtained from Sprague-Dawley fetuses at embryonic stage E15 and transduced with either GFP and MNTS1 constructs (MNTS1-NPCs) or with a GFP construct alone (control GFP-NPCs). Adult rats received moderate fluid percussion-induced TBI or sham surgery. Animals were transplanted 1 week later with either control GFP-NPCs, MNTS1-NPCs, or injected with saline (vehicle). Five weeks after surgery, animals were evaluated for hippocampal-dependent spatial memory and then sacrificed for immunohistochemical analyses. Six weeks after TBI, we observed significant survival and neuronal differentiation of MNTS1-NPCs, as well as injury-activated migration towards contused brain regions. NPCs displayed long processes with spine-like formations that extended into cortical and subcortical structures, including the hippocampus and contralateral hemisphere. Transplanted NPCs, irrespective of transduction profile, conferred significant preservation of pericontusional host tissues and enhanced endogenous hippocampal neurogenesis in the posttraumatic brain. Furthermore, NPC transplantation significantly improved spatial memory capacity on the hippocampal-dependent Morris water maze task. Transplant recipients exhibited escape latencies approximately half that of injured vehicle controls. Our findings support the potential of NPC transplantation and multineurotrophin therapy to enhance endogenous neuroreparative responses, and therefore may be an effective treatment for TBI.

Key words
adult hippocampal neurogenesis, learning and memory, neural progenitor cell transplantation, neuroprotection, traumatic brain injury

T1-11

EARLY HINDLIMB UNLOADING PRODUCES MALADAPTIVE PLASTICITY THAT LIMITS FUNCTIONAL RECOVERY AFTER SPINAL CORD INJURY (SCI)

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Partial weight bearing gait training for SCI induces adaptive plasticity and/or inhibits maladaptive spinal cord plasticity to promote functional recovery and re-organization of spinal reflex circuits. Weightless conditions such as prolonged bed rest in chronic SCI are thought to facilitate maladaptive spinal cord plasticity, leading to exaggerated withdrawal reflexes that can interfere with locomotor recovery. Hence, it has been suggested that appropriate shaping of loading-related spinal plasticity contributes to recovery in chronic SCI. However, the specific mechanisms by which loading and unloading shape spinal plasticity early after SCI remain poorly understood. We investigated hind-limb unloading (HU) early after SCI using adult female SD rats subjected to mild bilateral SCI (50 kdyn IH device) at T9. Groups were 1) chronic HU by tail suspension, and 2) normal loading controls. The HU group was returned to normal loading conditions at 2 wks and all animals were observed for 8 wks post-SCI. Assessments included: 1) Locomotor recovery using the BBB and kinematics, 2) reflex modulation using H-reflex testing of the plantaris muscle at 8 wks, 3), tissue biochemistry, and 4) unbiased high-resolution robotic confocal microscopy for plasticity-related changes. HU early after SCI impaired locomotor recovery and produced over-excitation of spinal reflex circuits. Biochemical and confocal microscopic studies into the substrates of this plasticity are ongoing. Our findings suggest that complete limb unloading early after SCI produces maladaptive spinal cord plasticity that impairs functional recovery. Our data suggest that loading-related spinal plasticity early after SCI plays an essential role in functional recovery.

Key words
loading, maladaptive spinal plasticity, recovery of function, synaptic plasticity

T1-12

INCREASED NODOSE GANGLION EXPRESSION OF CCK, CCK-1R, AND TRPV1 AND THE PATHOPHYSIOLOGY OF VAGAL AFFERENT DYSFUNCTION

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Spinal cord injury (SCI) causes immediate changes to gastrointestinal (GI) tract physiology. Parasympathetic control from the esophagus to the proximal colon is modulated by vago-vagal circuits which remain anatomically intact following SCI. Our previous reports indicate that SCI reduces gastric reflexes and vagal afferent sensitivity to GI peptides such as cholecystokinin (CCK). Furthermore, mesenteric hypoperfusion initiates a GI inflammatory response. Evidence in other models of GI dysfunction suggests that inflammatory mechanisms co-activate the transient receptor potential vanilloid type 1 receptor (TRPV1) that, in turn, contributes to the symptomatology of GI dysregulation. We tested the hypothesis that acute SCI induces molecular and neurophysiological alterations in gastric vagal afferents, cell bodies of which reside in the nodose ganglion, through the increased expression of TRPV1 and CCK and reduction in expression of CCK-1 receptor (CCK-1r). We used qRT-PCR to quantify the levels of CCK, CCK-1r, and TRPV1 in the nodose ganglia and inflammatory markers in the proximal colon at 1-day, 3-days, and 7-days post-SCI. Neurophysiological recordings were used to quantify the sensitivity of gastric vagal afferents to ligands of CCK-1r and TRPV1. Our data show a significant elevation of inflammatory markers within the proximal colon. Nodose ganglion expression of CCK and CCK-1r was significantly elevated as was expression of TRPV1. In Inactin-anesthetized rats, SCI resulted in the predicted reduction of mean arterial blood pressure. Low doses of CCK-8s provoked similar peak and mean vagal afferent firing, while preliminary data suggest an increased sensitivity to the TRPV1 agonist capsaicin following SCI. Our data are similar to the altered neurochemical phenotype of nodose ganglion neurons following vagal axotomy. The increase in CCK-1r may represent diminished receptor trafficking and needs further study. We conclude that an increase in inflammatory mediators in our model of SCI provokes TRPV1-mediated changes in vagal afferent signaling. Support: NS 49177, NS 87834.

Key words
cholecystokinin, gastrointestinal, nodose ganglion, TRPV1, vagus

T1-13

PERIPHERAL NOCICEPTIVE INPUT OVERDRIVES AMPA RECEPTOR ACTIVITY TO PRODUCE MALADAPTIVE PLASTICITY AFTER SPINAL CORD INJURY (SCI)

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Human SCI patients typically present with concomitant injury from the traumatic event, which likely sends a barrage of nociceptive input to the injured cord. Little is known about the effect of nociceptive input from concomitant injuries on plasticity in the injured spinal cord. Prior work has shown that intermittent nociceptive stimulation (INS) delivered below a complete SCI in rats produces hyperexcitability and undermines spinal training through unknown mechanisms. The dysregulation/overexpression of AMPA receptors following neural insult can lead to saturation of synaptic plasticity, excitotoxicity, and cell death. The current experiments assess the role of AMPA receptors in the impairing effects of INS in the injured cord. Rats with complete T2 spinal transections were given 6 min of INS to the tail (or unstimulated restraint), after which cords were harvested at 20 min or 2 hr post-stimulation. Western blot analysis revealed that INS rapidly increases GluA1 phosphorylation and plasma membrane expression, while reducing GluA2. Automated confocal image analysis of motor neurons revealed that INS increases GluA1 expression at extrasynaptic and synaptic sites in a sustained manner. GluA2 initially decreased extrasynaptically, and later decreased at synapses in response to INS. As GluA2 is the AMPA receptor subunit that mitigates calcium permeability, postsynaptic reduction suggests that Ca^{2+} permeable AMPA receptors (CP-AMPARs) may dictate functional

plasticity after SCI. To test the role of CP-AMPARs on spinal-mediated behavioral plasticity, we delivered the specific CP-AMPAR antagonist Naspm or vehicle following INS, and tested for adaptive plasticity using a spinal instrumental learning assay. Naspm restored adaptive learning. These findings highlight 1) the vulnerability of the injured spinal cord, 2) the capacity for nociceptive input to produce maladaptive plasticity after SCI, 3) the critical involvement of CP-AMPARs in activity-dependent spinal plasticity and 4) the nociception-induced loss of adaptive functional recovery after SCI. (Supported by NIH-NS-038079, NIH-NS-069537, NIH-NS-067092).

Key words
AMPA receptor, nociception, spinal plasticity

T1-14

NEUROPROTECTIVE EFFECTS OF PAM3-CSK4 IN SPINAL CORD INJURY

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Toll-like receptor 2 (TLR2) plays a protective role following spinal cord injury (SCI); however, the TLR2-mediated cellular and/or molecular mechanism(s) remains unclear. One possibility is that TLR2 signaling modulates activation of macrophage/microglia and their subsequent pro-inflammatory responses following injury. We hypothesized that following SCI, the synthetic TLR2-specific agonist Pam3-CSK4 could alternatively activate a neuroprotective macrophage/microglia phenotype and improve neurological outcomes. In this study, we assessed the effect of Pam3-CSK4 on 1) axonal retraction and secondary axonal degeneration; 2) macrophage/microglia immune functions; and 3) locomotive recovery. We first used an *ex vivo* laser-induced SCI (LiSCI) model to visualize myelinated axons responses after SCI in real-time with Pam3-CSK4 or control. We then used a T9/10 moderate contusion SCI to evaluate whether Pam3-CSK4 alters microglia and/or macrophage subset dynamics and/or their functions (6-color flow cytometry) as well as neurological recovery outcomes (Basso Mouse Scale). We found Pam3-CSK4 tended to inhibit axonal retraction/dieback in *ex vivo* spinal cord isolates after LiSCI. Moreover, Pam3-CSK4 decreased secondary axonal degeneration. Our flow cytometry results indicated Pam3-CSK4 did not alter the predominant pro-inflammatory M1 macrophage response which is typical for contusion SCI; however, it significantly down-regulated inducible nitric oxide synthase (iNOS) production in these cells. Characterization of microglia responding to contusion SCI using the same M1- and anti-inflammatory M2-associated markers revealed the major microglia subset population exhibited a M2-like phenotype that was functionally heterogeneous than macrophages. Nonetheless, similar to M1 macrophages, Pam3-CSK4 significantly decreased iNOS production in these M2-like microglia. Finally, Pam3-CSK4-treated mice showed greater functional recovery after SCI compared to control-treated mice. Overall, our data indicates that Pam3-CSK4 may improve neurological recovery following SCI by down-regulating inflammatory macrophage/microglia responses and modulating the extent of axonal injuries. This research is supported by funding from the PVA Research Foundation (grant 2934) and NIH (P30 GM103507).

Key words
axon, macrophage, microglia, Pam3-CSK4, SCI, TLR2

T1-15

RHOA/RHO KINASE REGULATES CPLA2 ACTIVATION IN SPINAL CORD NEURONAL TOXICITY INDUCED BY TNF-α AND GLUTAMATE

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Activation of RhoA/Rho kinase leads to growth cone collapse and neurite retraction. Although RhoA/Rho kinase inhibition has been shown to improve axon regeneration, remyelination and functional recovery, its role in neuronal death remains unclear. To determine whether RhoA/Rho kinase play a role in neuronal death, we investigated the relationship between RhoA/Rho kinase and cytosolic phospholipase A_2 ($cPLA_2$), a lipase that mediates inflammation and cell death, using an *in vitro* spinal cord neuronal death model. We found that co-administration of TNF-α and glutamate induced spinal neuronal death and activation of RhoA, Rho kinase and $cPLA_2$. Inhibitors of RhoA (CT04), Rho kinase (Y27632) and $cPLA_2$ (ATK) significantly reduced cell death by 33%, 52% and 43%, respectively ($p < 0.001$). Additionally, RhoA and Rho kinase inhibition significantly down-regulated $cPLA_2$ activation by 46% and 35%, respectively ($p < 0.01$). RhoA and Rho kinase inhibition also reduced the release of arachidonic acid (AA), a downstream substrate of $cPLA_2$. Co-immunoprecipitation (Co-IP) assay showed that ROCK1 or ROCK2, two isoforms of Rho kinase, bound directly with the active phospho-$cPLA_2$. Moreover, application of lysophosphatidic acid (LPA), a small GTPase Rho activator, activated Rho kinase and $cPLA_2$ and induced spinal cord neuronal death *in vitro*. Such cell death, however, was markedly reduced in postnatal cortical neurons isolated from $cPLA_2$ knockout C57BL/6 mice. Taken together, our results suggest that RhoA/Rho kinase may play a role in mediating neuronal death by regulating $cPLA_2$ activation.

This work was supported in part by National Institutes of Health NIH 1R01 NS059622.

Key words
cell signaling, cytosolic phospholipase A2, RhoA, Rho kinase

T1-16

18F-FDG PET IMAGING OF RAT SPINAL CORD INJURY SHOWS DEPRESSED GLUCOSE UPTAKE CORRELATING WITH LESION VOLUME & FUNCTIONAL RECOVERY

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The use of non-invasive markers of neurological outcome after spinal cord injury (SCI) are essential to predicting future outcome for patients and detecting responses to therapy and treatments. SCI results in acute reduction in neuronal and glial cell viability near the injury site and disruption in axonal tract integrity, as well as delayed but prolonged increase in glial activity and inflammation, all of which can influence glucose uptake. Positron emission tomography (PET)-based measurements of glucose uptake may serve as a novel biomarker for SCI. This study aimed to determine the glucose uptake pattern in the spinal cord after moderate SCI and correlate these findings with neuronal

viability, functional recovery, and glial activation. Briefly, adult male rats were subjected to a moderate contusion SCI and PET imaging with [^{18}F]Fluorodeoxyglucose (^{18}F-FDG), which was performed prior to injury and at 6 and 24 h and 15 days post-injury (dpi). Locomotor function was assessed at 2 and 14 dpi using the Basso, Beattie, and Breshnahan (BBB) scale, the ladder walk and modified cat walk tasks. Histology was performed at 16 dpi. Using region of interest (ROI) analysis with reference region normalization, ^{18}F-FDG PET imaging revealed that moderate contusion SCI significantly depressed glucose uptake in comparison with sham-injured and naïve controls at 6 h post-injury, followed by a gradual return to post-injury uptake by 15 dpi. Further, the degree of depressed glucose uptake at 6 h post-injury was correlated with lesion volume ($p = .0071$) and functional impairment at both acute (BBB function, 2 dpi, $p = .0085$) and delayed time points (ladder walk, 15 dpi, $p = .0252$). These results show that moderate SCI results in an observable depression in spinal cord glucose uptake using ^{18}F-FDG PET that may be predictive of histological and functional outcomes.

Key words
contusion injury model, glucose uptake, PET imaging, spinal cord, spinal cord injury

T1-17

HIGHER MEAN ARTERIAL BLOOD PRESSURES FOLLOWING HUMAN SPINAL CORD INJURY CORRELATE WITH GREATER NEUROLOGICAL RECOVERY

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Current guidelines for the care of patients with acute spinal cord injuries (SCIs) recommends maintaining MAP values of 85–90 mmHg following SCI, however little evidence supports this recommendation. We sought to better inform the relationship between MAP values and neurological recovery.

Physiological data was collected every minute (q1) from ICU monitors on 100 SCI patients over a 6 y period. 73 of these patients had AIS grades determined by physical examination on admission and at time of hospital discharge. The proportion of MAP values below threshold were calculated for values from 120 mmHg to 40 mmHg in 1 mmHg increments; these thresholds were explored within 1 d, 3 d, 5 d and 7 d of ICU admission.

A total of 994,875 q1 minute arterial line blood pressure measurements were recorded for the included patients amidst 1,688,194 minutes of recorded observation. Higher MAP values in the first 7 d were consistently associated with greater neurological recovery. The proportion of MAP values below a threshold of 85 – 90 mmHg robustly distinguished patients achieving a 1-point AIS grade improvement from those achieving 2 or 3 points of improvement. Patients with no AIS grade improvement had a greater proportion of MAP recordings below 100 mmHg than those who improved one AIS grade. Number of measures below 85 mmHg were significantly different in each outcome group ($p < 0.0001$).

This study provides strong evidence supporting a correlation between MAP values and neurological recovery. It does not, however, demonstrate a causal relationship. It supports the notion of MAP thresholds in SCI recovery and the highest MAP values correlated with the greatest degree of neurological recovery. The results are concordant with current guidelines in suggesting that MAP thresholds >85 mmHg may be appropriate following acute SCI.

Key words
blood pressure, outcome, spinal cord injury

T1-18

THE EFFECTS OF MYELIN RETRACTION AND DETACHMENT ON SIGNAL CONDUCTION IN A COMPUTATIONAL MODEL OF DAMAGED AXONS

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Mapping the relationship between injury mechanics, structural damage and functional outcomes in patients with spinal cord injury is important for identifying potential treatment targets. Computational models of the CNS augment animal and in vitro models by providing tools to evaluate the effects of specific structural changes after injury on function. Mild stretch injury of axons was shown to induce retraction and detachment of myelin around the nodes of Ranvier resulting in the exposure of fast potassium channels in the juxtaparanodal areas and reduction of the periaxonal resistivity. The aim of this study was to determine the effects of myelin retraction and detachment on action potential propagation along axons. A single motor neuron axon ($\varphi = 10$ um) based on the McIntyre's model of a mammalian motor nerve (McIntyre 2002) was modeled in NEURON. Fast potassium channels were implemented in the juxtaparanodal areas. To simulate the effect of myelin retraction, a damaged demyelinated area was inserted between the nodes (0.5 um) and shortened paranodal areas. The effect of myelin detachment has been simulated by a reduction in periaxonal resistivity (70 ohm-cm) in the paranodal and juxtaparanodal areas. Changes in action potential amplitude and conduction velocity were measured for isolated changes in nodal length, periaxonal resistivity, and potassium channel activity and simultaneous alternation of all injury parameters. Our results show that increasing the nodal length up to 1.5 um to simulate myelin retraction decreased the conduction velocity by 15% compared to the intact axons (40 m/s) and induced a small change (<3%) in action potential amplitude. Reducing either of paranodal or juxtaparanodal resistivity by 99% reduced conduction velocity by 45% and 35% respectively whereas peak action potential changed less than 25%. However, 70% simultaneous reduction in both paranodal and juxtaparanodal periaxonal resistivity stopped action potential generation. The post-injury axonal functionality is most affected by the detachment of myelin in the paranodal and juxtaparanodal regions when retraction and detachment are modeled simultaneously.

Key words
axonal injury, computational modeling, function, myelin

T1-19

NORBNI DOSE-DEPENDENTLY BLOCKS THE ADVERSE EFFECTS OF INTRATHECAL MORPHINE ADMINISTRATION FOLLOWING SCI

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Opioids are one of few effective analgesics for the treatment of pain following spinal cord injury (SCI). Unfortunately, we have shown that morphine administered in the acute phase of SCI, irrespective of the route of administration, compromises recovery of locomotor function, increases mortality and pain reactivity, and suppresses weight gain in a rodent contusion model (Hook et al., 2007, 2009, 2011). These adverse effects appear to depend on activation of the kappa opioid receptor (KOR). Selective activation of the KOR, using GR89696, undermined locomotor recovery and decreased weight gain. In the current study, we

tested whether activation of the KOR is *necessary* to produce the adverse effects of morphine using norBNI, a selective KOR antagonist. Subjects received a moderate spinal contusion (T12), and an intrathecal cannula was implanted. Baseline locomotor function (BBB) and pain reactivity (tail-flick) were assessed 24 hours following injury. Subjects were then pretreated with norBNI (0, .08, or .32 μmol), followed by morphine (0 or .32 μmol). Pain reactivity was re-assessed 30 minutes after drug treatment. Locomotor recovery was evaluated across a 21-day period, with additional tests of motor and sensory function conducted after day 21. Our results show that pretreatment with norBNI blocks the morphine-induced effects on recovery in a dose-dependent manner. At higher doses, norBNI eliminates morphine's adverse effects on recovery, but analgesia is also abolished. Conversely, at low doses, analgesia is maintained, but the adverse effects persist. This suggests that activation of the KOR system is necessary and sufficient for morphine-induced attenuation of recovery. However, as the protective dose of norBNI also diminished analgesic efficacy, simply blocking KOR activity is not sufficient for improving the efficacy and safety of clinical opioid use. Further understanding of the specific molecular changes induced by KOR activation is necessary to improve pain management strategies and facilitate functional recovery after SCI. Research support: Grant DA-031197, NIDA Drug Supply Program, & Mission Connect (TIRR Foundation).

Key words
KOR, locomotor function, norBNI, opioids

T1-20

AXONAL STRETCH INJURY RESULTS IN A POTENTIAL REDISTRIBUTION OF PHOSPHORYLATED TAU FROM AXONS TO THE SOMA AND DENDRITES

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Both single and repetitive traumatic brain injury (TBI) have been shown to induce abnormal aggregation of hyperphosphorylated tau comprising neurofibrillary tangles (NFTs), one of the hallmark pathologies of chronic traumatic encephalopathy. However, it has remained unknown how the axonal protein, tau, accumulates in the cell soma after TBI. Here, we examine the temporal effects of traumatic axonal injury (TAI) on tau phosphorylation levels within neuron compartments using a well-characterized in vitro model.

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 only region was rapidly stretched via mechanical parameters based on clinical TBI. Cells were immunocytochemically analyzed at 1, 24 and 48 hrs post injury for ankyrin-G, total tau and tau phosphoepitopes AT8, AT270 and S404.

By 1 hr following axonal stretch injury, decreases in axon initial segment (AIS) length and axonal total and phospho-tau immunoreactivity levels were observed. Concomitantly, increases in total and phospho-tau immunoreactivity levels were observed in the cell-soma and dendrites. Cell-somal phospho-tau levels continued to increase over 48 hrs post-injury. Translocation of phospho-tau S404 into dendrites was observed within 1 hr, whereas phospho-tau AT8 was only observed after 24 hrs. The protein synthesis inhibitor Emetine reduced cell-somal increases in total and phospho-tau immunoreactivity levels.

Although specific mechanisms inducing the chronic formation of post-traumatic NFTs remain elusive, the present data provides potential sources of acute increases of phospho-tau in neuronal soma and dendrites, including: 1) a reduction in the AIS diffusion barrier resulting in a translocation of total tau/phospho-tau from the axon into the soma, and 2) de novo tau protein synthesis and accumulation in the soma.

Supported by DOD grant, PT110785 and NIH grant NS056202.

Key words
axon stretch, phosphorylated tau, traumatic axonal injury

Open Communications

OC1-01

HYPEROXIC VERSUS NORMOXIC RESUSCITATION IN A RAT POLYTRAUMA MODEL OF TBI PLUS HEMORRHAGIC SHOCK

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Many civilian and warfighter TBI victims experience additional injuries, including those that result in hemorrhagic shock (HS). Reduced O_2 delivery that accompanies HS may exacerbate TBI. This study tested the hypothesis that inspiration of 100% O_2 during resuscitation following TBI and HS reduces brain lesion volume and improves neurologic outcome compared to what occurs in the absence of supplemental O_2.

Brain injury to isoflurane anesthetized adult male rats was induced by controlled cortical impact (CCI) at a depth of 2.0 mm. HS was then induced by extracting blood until the target range of 35–40 mm Hg for mean arterial pressure was reached and maintained for 30 min. The HS phase was followed by a one hr ''Pre-Hospital'' fluid resuscitation phase utilizing infusion of Hextend. This period was followed by a one hr ''Hospital Phase'' when shed blood was returned to rats. Rats were randomized on the day of surgery to 4 groups with 10 rats per group: A. Sham Normoxic. B. Sham Hyperoxic. C. Polytrauma Normoxic. D. Polytrauma Hyperoxic. Normoxic animals inspired room air and Hyperoxic animals inspired 100% O_2 during the resuscitation phases. Neurobehavioral tests were conducted weekly until the rats were perfused with fixative at 30 days post injury (dpi). Brain sections were stained with Fluorojade B (FJB) and used for stereology-based quantification to estimate contusion plus penumbral cortical volumes.

Survival was significantly greater following hyperoxic (84%) compared to normoxic resuscitation (57%). Composite neuroscores were higher with normoxic resuscitation at 21 dpi and balance beam foot faults were significantly lower with normoxic resuscitation at 14 dpi. There was no difference in cortical pathology between the Normoxic and Hyperoxic polytrauma groups.

The survival and general health of rats following CCI plus HS was greater following hyperoxic resuscitation. In contrast, neurologic outcomes were better following normoxic resuscitation.

Acknowledgments
This work was supported by USAMRMC Awards W81XWH-09-2-0187 and W81XWH-07-2-0118.

Key words
hyperoxia, normoxia, polytrauma, shock

OC1-02

GLOBAL METABOLOMICS PROFILING REVEALS METABOLIC DYSREGULATION, OXIDATIVE STRESS AND NEUROTRANSMISSION ALTERATION AFTER CONCUSSION

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Concussion is a mild form of trauma brain injury (TBI) that can lead to long-term neurological deficits, and poses a risk factor for recurring concussions. This study was designed to establish a temporal biochemical profile following single or repetitive concussions, and to identify biochemical processes that contribute to injury-associated neuropathologies. Adult Sprague-Dawley rats were randomly assigned into three groups: sham (anesthesia), single projectile concussive impact (sPCI), and repeated PCI (rPCI; 4 consecutive PCIs spaced 1 hr apart). Ipsilateral frontal cortices were collected at 30min, 2 hr, 6 hr, 24 hr, 72 hr and 7 days post-sPCI, and at 2 hr post-rPCI (n = 6/group/time-point). Mass spectrometry-based metabolomics profiling revealed increased anaerobic glycolysis indicated by significantly elevated glucose levels and glycogen metabolites in both sPCI and rPCI tissues compared to sham controls. Significantly elevated levels of glucose-6-phosphate and pentose phosphate pathway (PPP) metabolites were only detected in the rPCI tissues, suggesting an increase of glucose flux through PPP for tissue repair. Accompanied by higher levels of pyruvate and lactate, all PCI samples exhibited significantly elevated levels of the tricarboxylic acid cycle (TCA) intermediates citrate and alpha-ketoglutarate, but lower levels of succinate compared to sham controls, suggesting impaired mitochondrial oxidation and free radical production. Relevant to this, both sPCI and rPCI tissues exhibited significant reduction of carnosine and glutathione levels, indicative of oxidative stress. Further, gamma-aminobutyric (GABA) and acetylcholine levels trended higher in both sPCI and rPCI tissues following injury. A significant increase of glutamine was accompanied by lower levels of glutamate in both sPCI and rPCI tissues, suggestive of excitotoxic injury. Overall, PCI significantly altered the metabolic profile of the brain tissue, induced oxidative stress and neurotransmitter changes. More importantly, global metabolomics profiling was able to identify biochemical processes that reflect an increased susceptibility to injuries following rPCI, demonstrating that repetitive concussions exacerbate outcome when occurring within a window of cerebral vulnerability.

Key words
concussion, glucose metabolism, metabolomics, oxidative stress

OC1-03

MITOCHONDRIA ASSOCIATED MICRORNA EXPRESSION IN HIPPOCAMPUS FOLLOWING TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) is a major cause of death and disability. However, the molecular events contributing to the pathogenesis are not well understood. Mitochondria serve as the powerhouse of cells, respond to cellular demands and stressors, and play an essential role in

cell signaling, differentiation, and survival. There is clear evidence of compromised mitochondrial function following TBI, however, the underlying mechanisms and consequences are not clear. MicroRNAs (miRNAs) are small non-coding RNA molecules that regulate post-transcriptional gene expression, and function as important mediators of neuronal development, synaptic plasticity, and neurodegeneration. Several miRNAs are altered following TBI, however, the involvement of mitochondria in modulating miRNA activity is unknown. Here, we present evidence supporting the presence of miRNA associated with hippocampal mitochondria, as well as changes in miRNA expression levels following a cortical contusion injury (CCI) in rats. Specifically, we found that the miRNA processing proteins Argonaute (AGO) and Dicer are present in mitochondria from uninjured rat hippocampus, and immunoprecipitation of AGO associated miRNA from mitochondria suggests the presence of functional RNA-induced silencing complexes. Interestingly, RT-qPCR miRNA array studies revealed that a subset of miRNA is enriched in mitochondrial relative to cytoplasm. At 12 hr following CCI, several miRNA are significantly altered in hippocampal mitochondria and cytoplasm. In addition, levels of miR-155 and miR-223, both of which play a role in inflammatory processes, are significantly elevated in both cytoplasm and mitochondria. We propose that mitochondria serve as a platform for miRNA function and play an important role in regulating miRNA activities in response to cellular demand and stressors such as that observed following TBI. Supported by the Morton Cure Paralysis Fund (JES), PHS grants AG028383, NS085830 and NS061933 (PTN), and NS062993 (PGS).

Key words
cortical contusion injury, hippocampus, microrna, mitochondria

OC2-01

BLAST INJURY EXACERBATES NEUROPATHOLOGY AND IMPAIRS VISUAL FUNCTION IN A TRANSGENIC APPSWE-PSEN1DE9 MOUSE MODEL OF AD

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The purpose of this study was to determine if blast-mediated TBI accelerates neurodegeneration in APPswePSENd19e mice (APP-PSEN), which have a genetic predisposition to develop an Alzheimer's disease (AD) phenotype characterized by deposition of Amyloid-beta (Aβ). We also examined if increased Aβ accumulation was associated with exacerbated functional and structural *in vivo* retinal outcomes which could serve as non-invasive metrics for evaluation of brain pathology after injury.

Mice were exposed to a single blastwave: 150 kPa, 10 ms positive peak duration. Retinal function and structure were assessed two months following injury using the pattern electroretinogram (pERG) and optical coherence tomography (OCT), respectively. Mice were then euthanized and Aβ concentration and plaque load were assessed in the hippocampus (HPC) and cortex (CTX).

Compared to sham blast-exposed littermates, blast-injured APP-PSEN mice had significant reductions in pERG amplitudes ($19.92 \pm 1.91\ \mu$V and $11.13 \pm 0.97\ \mu$V, respectively; $p < 0.01$) and retinal ganglion cell (RGC) complex thickness ($76.71 \pm 2.50\ \mu$m and $64.65 \pm 3.31\ \mu$m, respectively, $p < 0.01$) two months after blast exposure. Blast-exposed APP-PSEN mice also had fewer axons in the optic nerve as well as substantial increases in soluble and insoluble Aβ40 and Aβ42 concentrations and a 2–6 fold increase in Aβ plaque load in the HPC and CTX compared to sham-blast-exposed littermates.

The extent of both visual impairments and increases in brain Aβ levels in APP-PS mice were exacerbated two months after blast TBI. Visual deficits in APP-PSEN mice manifested twice as fast as we have reported using the same injury in wild-type mice. These data suggest that analyses of retinal structure and function could serve as *in vivo* biomarkers to evaluate the extent of blast-mediated neuronal damage either alone or in relation to Aβ-induced neurodegeneration.

Funding
VA RR&D MERIT Award 1I01RX00095.

Key words
Alzheimer's disease, vision

OC2-02

EFFICIENT ESTIMATION OF BRAIN STRAIN RESPONSES IN CONTACT SPORTS USING A PRE-COMPUTED MODEL RESPONSE ATLAS

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Finite element models of the human head are playing an important role in investigating the mechanisms of traumatic brain injury, including sports concussion. A critical limitation, however, is that they incur a substantial computational cost (typically hours on a modern multi-core computer or even a super computer) to simulate a single impact. Consequently, model-based brain injury studies have been focused on single head impacts to date and current simulation schemes are impractical to investigate the significance of repetitive head blows especially on a large scale. In this study, we evaluated the feasibility of a pre-computed model response atlas (pcMRA) to significantly increase the simulation efficiency using isolated rotational acceleration impulses parameterized with four independent variables (peak magnitude (a_{rot_p}) and duration, and rotational axis azimuth and elevation angles). The parametric space was sampled by combining each variable with values determined from on-field measurements to serve as the training dataset (a_{rot_p} was limited to 1.5–4.5 krad/s^2, approximately corresponding to the 50th and 95th percentile magnitudes in ice-hockey). Using randomly generated testing datasets with a_{rot_p} range 0.5–7.5 krad/s^2 (approximately from 25th percentile sub-concussive to 95th percentile concussive a_{rot_p} in college football, or up to $\sim$99th percentile a_{rot_p} in ice-hockey), the pcMRA interpolation (a_{rot_p} range 1.5–4.5 krad/s^2) achieved a 100% success rate based on element-wise differences in accumulated peak strain (e^p; relative to directly simulated ground-truths or injury-causing thresholds according to a "double-10%" criterion, i.e., volume fraction of large element-wise differences ($>10\%$) for the whole-brain was $<10\%$) or average regional e^p in generic regions (difference $<10\%$). Further, (nearly) excellent performance was maintained in extrapolation for out-of-range a_{rot_p} impulses. The computational cost to estimate element-wise whole-brain or regional e^p using the pcMRA was 6 sec and <0.01 sec, respectively, while it was $\sim$30 min to directly simulate a 25 ms impulse. These findings suggest the feasibility for pcMRA to substantially increase the throughput in head impact simulation without significant loss of accuracy and, therefore, its potential to accelerate the exploration of the mechanisms of sports concussion.

Key words
contact sports, Dartmouth head injury model, finite element modeling, pre-computation, repetative head impacts

OC2-03

A RABBIT MODEL OF PEDIATRIC TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) is a common cause of disability in childhood, yet the mechanisms responsible for its complex pathologies remain largely unknown. A limitation of pediatric rodent models of TBI is that they often do not demonstrate the spectrum of motor and cognitive deficits seen in pediatric TBI patients. To address this, we developed a model of pediatric TBI in New Zealand rabbits that mimics pediatric brain development better. On postnatal day 5–7 (P5-7), rabbits were injured with controlled cortical impact (CCI) (6mm impactor tip; 5.5 m/s, 2 mm depth, 50 msec duration). Rabbits from the same litter served as control (no injury) and sham (craniotomy alone). Functional abilities (cranial nerve, motor and sensory functions) and activity levels (open field) were measured 24-h and 5-d after surgery. Maturation level was monitored daily. The cognitive tests, spontaneous alternation in T-maze and novel object recognition, were carried out during P14-26. Animals were sacrificed 3, 7 and 21 days after TBI for evaluating lesion volume and microglia (IBA1 staining). Significant decreases in the overall motor functions, such as suck and swallow, head movements and hops, was noted 24–48 hours after TBI. In addition, TBI kits showed a delayed achievement of normal developmental milestones, such as eye opening, and loss of cliff-avoidance. Significant cognitive deficits were noted in the TBI kits with lower percentage of correct alternation rate in the T-maze ($n = 8$-10/group; $p < 0.001$) and less discrimination between novel and old objects ($p < 0.01$) when compared with controls and shams. Lesion volume increased from 10% at 3 days to 30% at 7 days after injury, indicating ongoing secondary injury. Activated microglia were noted at the injury site and also in white matter regions (periventricular region and internal capsule) of both the ipsilateral and contralateral hemispheres. The short-term and long-term impairments of this model are comparable to those reported clinically, providing a novel platform for evaluating neuroprotective therapies in pediatric TBI.

Key words
developmental brain injury, microglia, pediatric

OC3-01

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

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Autophagy is a lysosome-dependent intracellular degradation pathway, which plays a neuroprotective function in several neurodegenerative diseases. Although elevated autophagic markers have been reported after SCI, its mechanism, cell type specificity, and relationship with cell death remain unknown. In a rat model of moderate contusive SCI, we found increased levels of autophagy marker, LC3-II, by western blot and increased numbers of cells accumulating LC3-positive autophagosomes by immunohistochemistry (IHC), starting at 1 day after injury and continuing for up to 5 weeks. Initial accumulation of LC3 was accompanied by pronounced elevation in the levels of the autophagy substrate, p62. This indicates that the initial increase in markers of autophagy was due to defective lysosomal clearance of autophagosomes and their cargo. Accumulation of p62 was resolved by day 7 after SCI, and was associated with elevated levels of the lysosomal enzyme cathepsin D. Therefore, increase in the size and activity of the lysosomal compartment may help restore autophagy flux at that time. Furthermore, we used IHC to study cell type specificity of autophagy after SCI. LC3 preferentially accumulated in oligodendrocytes and microglia in the white matter, and co-localized with the neuronal cell marker NeuN in the gray matter. LC3 was especially pronounced at day 1 after SCI in motor neurons in the ventral horn. Since our data indicate that at that time autophagic clearance is blocked, we hypothesize that it may contribute to neuronal cell death. Consistently, we found that p62 labeled cells were also positive for apoptotic cell death markers, cleaved caspase 3 and caspase 12, indicating association between disrupted autophagy and cell death. Together, our data indicate that autophagic degradation is temporarily blocked and may contribute to neuronal cell death after SCI.

Key words
apoptosis, autophagy flux, p62, SCI

OC3-02

PROTEASE ACTIVATED RECEPTOR-MEDIATED MECHANISMS OF NEURAL INJURY

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Central nervous system injury, including that elicited by trauma, ischemia, infection, neurodegeneration or neoplasia, creates a complex wound manifesting with a cascade of secondary cellular and molecular responses that worsen the initial insult and limit repair and regeneration. Among the deregulated neurotoxic factors are serine proteases of the thrombolytic, fibrinolytic and kallikrein families, either as a result of elevations in endogenous cells, secretion by infiltrating immune cells or extravasation. Here we document changes in expression in kallikrein 6 and thrombin in a murine model of spinal cord contusion-compression injury and document key pathophysiologic activities impacting the development and progression of traumatic spinal cord injury (SCI), including oligodendrogliopathy, neuron degeneration, axonopathy, and astrogliosis. Importantly, we provide mechanistic evidence that the neurotoxic effects of kallikrein 6 are mediated by activation of select members of a G-protein coupled receptor family referred to as Protease Activated Receptors (PARs). PAR activation is induced by proteolytic cleavage within the extracellular N-terminus of the receptor revealing a cryptic tethered ligand that binds intramolecularly to induce intracellular signaling. Kallikrein 6 elicited PAR1-dependent dying back of oligodendroglial processes and suppression of myelin gene expression. PAR1, in addition to PAR2, were shown to play critical roles in kallikrein 6-mediated neuron injury, astrocyte stellation and secretion of the pro-inflammatory cytokine IL-6. Moreover, genetic deletion of PAR was associated with reductions in molecular signatures of injury in murine SCI, including decreases in markers of apoptosis (BIM), astrogliosis (GFAP, Vimentin) and Th1 pro-inflammatory cytokines (IL-6, IL1-β). These studies suggest that PARs or their protease agonists represent new modalities to moderate pathophysiological responses that occur in association with traumatic SCI and to foster an environment favorable to repair and regeneration.

Key words
demyelination, protease, spinal cord injury

OC3-03

DEVELOPMENT OF A CERVICAL SPINAL CORD CONTUSION MODEL IN NON-HUMAN PRIMATES

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A growing number of potential treatment approaches for spinal cord injury (SCI) have been developed using rodent models, but successful translation of treatments to human SCI has been fraught with challenges. An intermediate step in this process has been identified by the field supporting the use of a non-human primate (NHPs) model of preclinical SCI. Using finite element analysis to scale up a unilateral cervical contusion injury in the rat to NHPs, we have established a contusion injury protocol that has many features of human cervical SCI. Furthermore, this contusion model is supported by detailed behavioral, electrophysiological and anatomical outcomes. Under deep anesthesia, nine rhesus macaques received a unilateral contusion SCI at vertebral level C5 using a friction-free actuator (Model 200N LM1, Bose® Corp) with a 4mm diameter impounder. Impact parameters were pre-calibrated *in vitro* using a silicon-based surrogate cord, producing a wide range of injuries. Walking, climbing, and object manipulation were assessed during open-field testing in all subjects. Skilled hand function, electromyogram analysis, sensory testing, corticospinal tract tracing and magnetic resonance imaging were also performed in a subset of animals. A high correlation between peak force at impact and behavioral outcomes indicates the predictability of the method for producing controlled injuries that can be used to test treatments. Supported by NIH (R01-NS042291, R01-NS067092, F32-NS079030), VA (B7332R), & The CH Neilsen Foundation.

Key words
contusion injury, non-human primates, pre-clinical model, spinal cord injury

OC4-01

VIBRATION EXPOSURE LIMITS FOR NEUROTRAUMA PATIENTS DURING MEDICAL TRANSPORT: OVERVIEW

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Anecdotal observations in the field reported severe pain experienced by neurotrauma patients when subjected to bumpy and high vibration ground and air medical transport. The literature indicates that vehicle vibration due to medical transport may be affecting medical outcomes. The goals of our efforts are to (1) Characterize the effects of transport on a swine model of traumatic brain injury (TBI) and spinal cord injury (SCI), (2) Characterize the healthy human biodynamic response under similar transport modes, (3) Identify TBI/SCI biomarkers from behavioral, histological, imaging, and physiological measures, and (4) Develop the dose-response relationship and determine the vibration exposure limit for injured humans. The TBI mechanism is accomplished through blast exposure and the SCI is produced surgically similar to the University of British Columbia model. The TBI/SCI model is exposed to realistic ground and air medical transport scenarios. The tested animals are divided into four groups: (1) sham group, (2) TBI/SCI + transport, (3) TBI/SCI and 4) SCI + transport. Standard military medical transport procedures are practiced for immobilizing and securing the TBI/SCI model. Physiological measurements and vehicle vibration throughout the patient litter support system to include the animal model are recorded. X-ray images, MRI, and neurologic evaluation are conducted before and after each exposure. Various immunohistochemical and other CNS stains are used to validate astrocyte-released injury biomarkers in swine CSF. Vibration transmissibility of the patient support system in a military helicopter is measured using supine healthy humans. The transfer functions measured for the injured animals and the healthy humans are transformed to determine vibration exposure limit criteria relevant to neurotrauma patient transport.

Key words
immobilization, medical transport, vibration

OC4-02

DISRUPTION OF AUTOPHAGY FLUX FOLLOWING SPINAL CORD INJURY IN GFP-LC3 REPORTER MICE

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Autophagy is a lysosome-dependent intracellular degradation process. It plays an essential role in cellular homeostasis as well as a protective function against a variety of conditions, including neurodegeneration. Up-regulation of autophagy has been detected after SCI, but its mechanisms and function remain unknown. Additionally, processivity of autophagic degradation (flux), a crucial parameter that can radically alter the function of autophagy, has not been determined after acute SCI. We assessed levels of autophagy and autophagy flux after moderate contusion SCI in transgenic mice expressing autophagy reporter GFP-LC3. Our data indicated that autophagy marker LC3-II was increased starting 3 hours after injury and remained elevated for at least 8 days. Accumulation of autophagosomes was confirmed by direct imaging of GFP-LC3 in the injured spine sections. In the gray matter, autophagosomes primarily accumulated in the ventral horn motor neurons. In the white matter, GFP-LC3 signal accumulated in oligodendrocytes and their precursors, and in activated microglia. In addition to accumulation of GFP-LC3, in the same cells we also observed elevated levels of the autophagy substrate, p62 and of ubiquitinated proteins. This indicates that after SCI autophagosomes accumulate due to inhibition of autophagic degradation rather than increased biosynthesis. Levels of p62 and ubiquitinated proteins declined 1 week after injury, indicating that at that time autophagy flux is likely restored. Although under most conditions autophagy serves as a protective mechanism, when flux is blocked, it may contribute to cell death. Consistent with

contribution of defects in autophagy to acute neuronal loss, in ventral horn motor neurons we observed co-localization of GFP-LC3 signal with the marker of apoptotic cell death, caspase 12. Together our data indicate that after SCI in GFP-LC3 reporter mice autophagy flux is temporarily impaired and may contribute to motor neuron cell death.

Key words
autophagy, autophagy flux, GFP-LC3, transgenic mouse model

OC4-03

INHIBITION OF NOX2 REDUCES LOCOMOTOR IMPAIRMENT, INFLAMMATION AND OXIDATIVE STRESS AFTER SPINAL CORD INJURY

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Spinal cord injury (SCI) results in activation of the NADPH oxidase enzyme, inducing production of superoxide, a reactive oxygen species (ROS). As ROS play an integral role in inflammation and oxidative damage, we aimed to investigate the role of the NADPH oxidase 2 (NOX2) enzyme in post-SCI inflammation and functional deficits. We therefore performed moderate spinal cord contusion injury in adult male mice and administered the NOX2 specific inhibitor, gp91ds-tat, or scrambled-tat intrathecally immediately after impact. We then used flow cytometry, western blot, and immunohistochemistry to assess NOX2 activity and expression, inflammation, and M1/M2 microglia/macrophage polarization at 24 hours and 7, 21, and 28 days post-injury. The Basso mouse scale (BMS) was used to assess locomotor function at 24 hours post-injury and then weekly thereafter. Administration of the NOX2 specific inhibitor significantly reduced acute oxidative stress, as measured by immunohistochemistry for the DNA damage marker 8OHdG and western blotting for protein carbonylation, indicating a reduction in ROS production by gp91ds-tat. Further, gp91ds-tat administration resulted in a significant reduction in inflammatory cells, as measured by flow cytometry at 24 hours and 7 days post-injury. Further, at 24 hours post-injury, gp91ds-tat injection led to a reduction in the protein expression of NOX2 and the M1 marker CD86. However, by 28 days post-injury, there was no significant difference in number of microglia, macrophages, T cells or neutrophils between groups, suggesting that a single acute treatment does not induce chronic changes in the inflammatory response. Despite this, significant and long lasting improvements in motor function were observed in the BMS scores of gp91ds-tat treated mice in comparison to those that received the scrambled-tat. Based on our findings, we now conclude that inhibition of NOX2 significantly improves motor function, possibly by reducing inflammation and oxidative stress acutely after injury. NOX2 inhibition may therefore have true potential as a therapeutic after SCI.

Key words
microglia polarization, motor function, NADPH oxidase, oxidative stress

OC5-01

NEUROENDOCRINE-IMMUNE DYSFUNCTION IN INDIVIDUALS WITH POOR OUTCOME AFTER SEVERE TRAUMATIC BRAIN INJURY

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Bidirectional communication between the immune and neuroendocrine systems is not well understood in traumatic brain injury (TBI). Thus our objective was to characterize relationships between cerebrospinal fluid (CSF) cortisol and inflammation after severe TBI, and determine how this relationship differs by outcome. CSF samples were collected 0-5 d post-injury in 91 adults and analyzed for cortisol and inflammatory markers. Our primary outcome was Glasgow Outcome Scale (GOS) score at 6 months. Group-based trajectory analysis (TRAJ) delineated subpopulations with similar longitudinal cortisol profiles. Inflammatory markers whose individual relationship to outcome was mediated by cortisol TRAJ (IL-6, IL-10, sFas, sICAM-1, and TNF-α) made up a cumulative inflammatory load score (ILS). Covariate associations with ILS were explored concurrently with cortisol TRAJ, and showed age, diffuse axonal injury, and intracranial hemorrhage influenced ILS. As expected, cortisol TRAJ group membership mediated the relationship of this cortisol-specific ILS on outcome after controlling for age and GCS. Correlational analysis between mean cortisol levels and ILS were examined within each cortisol TRAJ group and by outcome. Within the low cortisol TRAJ, subjects with unfavorable outcomes displayed a negative correlation between ILS and mean cortisol ($r=-0.548$, $p=0.052$). Conversely, subjects with unfavorable outcome in the high cortisol TRAJ displayed a positive correlation between ILS and mean cortisol ($r=0.391$, $p=0.006$). Our results suggest unfavorable outcome after TBI may result from dysfunctional neuroendocrine-immune crosstalk. Importantly, the nature of inflammatory dysfunction, and presumed relationships with hypothalamic-pituitary-adrenal function, differs between cortisol TRAJ groups. Correlational analysis suggests bidirectional inflammatory marker transit after TBI, uniquely supporting current bidirectional characterization associated with neuroendocrine-immune crosstalk. The present data support evaluating targeted anti-inflammatory treatment strategies early after injury and investigating chronic changes in neuroendocrine-immune crosstalk during recovery.

Support
CDCR49 CCR323155; DODW81XWH-071-0701; NIH5P01NS030318.

Key words
cortisol, hypothalamaic-pituitary-axis, inflammation, interleukins, trajectory analysis, traumatic brain injury

OC5-02

PHASE II CLINICAL TRIALS OF CETHRIN IN ACUTE CERVICAL SPINAL CORD INJURY

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Spinal cord injury often results in lifelong paralysis. Axons damaged in the spine fail to regenerate, largely due to Rho activation by growth inhibitory proteins and inflammatory mediators. This Rho activation signals cytoskeletal disassembly and axonal growth cone collapse. Cethrin is a biologic drug derived from C3 transferase that prevents Rho activation and promotes axon regeneration in rat models of neurotrauma. A first-in-man, Phase I/IIa clinical study of Cethrin in acute complete spinal cord injury (AIS A) demonstrated that the drug was well tolerated and showed the potential to improve neurological recovery in a functionally meaningful manner. Participants in all Cethrin

dose groups improved an average of 16.4 ± 17.3 points from baseline in total motor score (TMS) and 12.2 ± 10.5 points in upper extremity motor score (UEMS) during the year after injury; participants in the best dose group improved 27.3 ± 13.3 points in TMS and 15.7 ± 5.5 points in UEMS. These trends are promising, given the 9.6–13.2 point TMS recovery and 8.8 – 9.6 point UEMS recovery seen in historical individuals. In addition, 31% of Cethrin-treated cervical participants converted two or more AIS grades in the year after injury, and 44% converted two or more motor levels. These trends also compare favorably with historical data: only 17% of historical individuals convert two or more AIS grades in the year following injury, and 24%–33% convert two or more motor levels. BioAxone is presently planning a placebo-controlled, randomized Phase IIb trial to further examine Cethrin in acute cervical spinal cord injury. The primary endpoint in this trial will be UEMS. Secondary endpoints will include established tests such as the Spinal Cord Independence Measure (SCIM), and newer tests such as the Capabilities of Upper Extremity Test (CUE-T) and the Graded Redefined Assessment of Strength Sensibility and Prehension (GRAASP). In addition, BioAxone is developing a questionnaire to assess the role of rehabilitation in the recovery of treated and placebo groups.

Key words
cervical, paralysis, regeneration, Rho, SCI, spinal cord injury

OC5-03

MULTIPLE PRIOR CONCUSSIONS ARE ASSOCIATED WITH SYMPTOMS IN HIGH SCHOOL ATHLETES

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Several recent studies have reported conflicting results as to whether or not multiple prior concussions are associated with differences in baseline computerized neurocognitive testing and symptom scores. The purpose of this study is to evaluate the association of prior concussion on baseline computerized neurocognitive testing in a large cohort of high school athletes.

This is a retrospective cohort study of student athletes from 49 Maine High Schools in 2010 who underwent baseline computerized neurocognitive evaluation with Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT®). As part of the ImPACT®, subjects reported a prior history of concussion as well as demographic information and a symptoms score. Subjects reporting a concussion within 26 weeks of baseline testing were excluded. We used linear regression to evaluate the association of prior concussion with baseline: 1) ImPACT® composite scores; 2) Symptom scores.

Six thousand seventy five subjects were included in the study, of whom 57% were male. The majority of athletes (85.3%) reported no prior history of concussion while 4.6% reported having sustained 2 or more prior concussions. On simple linear regression, increasing number of concussions was related to worse performance in verbal memory ($p = 0.039$) and higher symptoms scores ($p < 0.001$). On multivariate modeling, controlling for demographic factors, only the association with baseline symptom scale remained ($p < 0.001$).

In this large-scale, retrospective survey study, history of multiple prior concussions was associated with higher symptom burden but not baseline computerized neurocognitive testing.

Key words
baseline neurocognitive test, ImPact®Test, multiple concussion, self report, symptoms

OC6-01

REPORT OF LONGITUDINAL MRS AND DTI AFTER MODERATE/SEVERE PEDIATRIC TBI

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We present our findings on a prospective study of MRS and DTI measures in pediatric TBI patients acutely and at 1-year after injury.

Pediatric patients, ages 4 to 18, were enrolled if they sustained a moderate/severe TBI requiring admission to hospital, defined either as having a GCS score < 13 OR if evidence of intracranial injury on initial computed tomography scan. Patients underwent 3T MRI with DTI and proton MRS in the acute period (6–17 days post TBI), and at 1 year after injury. TBI and control regional DTI metrics (FA, ADC, AD, RD) and MRS ratios (NAA/Cr, NAA/Cho, Cho/Cr) for the initial and one year follow-up studies were compared and correlated to neurologic (PCPCS) and neuropsychological outcomes at 12 months, specifically general measures of memory utilizing the Children's Memory Scale (CMS: General Memory score), attention utilizing the Test of Everyday Attention for Children (TEA-CH: Teach G score), and the Wechsler Abbreviated Scale of Intelligence (WASI: Full Scale IQ).

We studied 58 children (43M/15F); mean age was 12.2 ± 3.5 yrs (5.2–17.9 yrs); initial GCS (Mild = 23; Moderate = 8; Severe = 27) and 54 control children; mean age 12.1 ± 3.3 yrs (5.5–17.4 yrs). Initial studies were done at 11.5 ± 3.4 days after injury and follow-up studies were done at 12.2 ± 3.5 months for TBI patients and 12.1 ± 3.3 months for controls. Total and regional NAA/Cr ratios and total, corpus callosal, parietal and temporal white matter mean FA and AD measures were 1) significantly reduced initially compared to controls; 2) were significantly correlated with neurologic outcomes, FSIQ and General Memory scores and 3) did not recover in patients with initial severe injury at 1 year.

Metabolite and DTI measures that remain reduced at one year after injury in patients with severe injury suggest that neuronal loss and axonal injury contribute to long term intellectual and memory deficits.
Support from NIH/NINDS:R01-NS054001.

Key words
diffusion tensor imaging, magnetic resonance spectroscopy, pediatric, traumatic brain injury

OC6-02

OPTIMIZING NEUROMODULATION FOR WALKING IN HUMAN INCOMPLETE SPINAL CORD INJURY

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Locomotor recovery occurs to some extent in humans with incomplete spinal cord injury (SCI) and this recovery can be augmented with

locomotor training. Recent attempts have been made in both animal and human studies to further augment locomotor functioning in SCI using afferent stimulation, either at the level of the dorsal roots using transcutaneous spinal cord stimulation (TSCS) or with peripheral nerve stimulation. The goal of this project was to develop a method to optimize the stimulation parameters used to best improve stepping in different individuals with incomplete SCI.

Tonic TSCS and/or phasic tibial nerve stimulation (TNS) was applied to subjects during stepping in the Lokomat gait orthosis at different frequencies (TSCS or TNS) and for different durations during different portions of the gait cycle (TNS). Stimulation occurred in an open-loop format initially and then was controlled based on force feedback from the Lokomat (less force needed from the robot was better) and on electromyography (EMG) from 8 leg muscles (the more appropriate the timing of muscle EMG, the better). The optimization algorithm then determined the best stimulation parameters to generate the most normal muscle activity and the least robotic forces.

We have found that TSCS can modulate stepping in a stimulation frequency dependent manner and can not only improve activation patterns between muscles, it can reduce pathological states like clonus. We also found that TNS was best at augmenting muscle activations and modulating force parameters when applied at frequencies above 75 Hz, for less than 15% of the gait cycle, and timed at the stance to swing transition.

With the development of optimization algorithms for neuromodulation, we should be able to individualize, and adjust based on ongoing recovery, a novel intervention to facilitate the nervous system that remains after incomplete SCI to best augment walking function.

Key words
human, locomotion, neuromodulation, robotics

OC6-03

INTRACRANIAL PRESSURE TREATMENT TAILORED TO TRANSCRANIAL DOPPLER-DERIVED COMPLIANCE AND PERFUSION

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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 48 h 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.

Key words
cerebral perfusion, compliance, goal-directed therapy, transcranial doppler

Poster Abstracts

A1-01

THE SURGICAL STRATEGY OF PENETRATING ORBITO-CRANIAL COMBINED INJURIES FROM HIGH TEMPERATURE LIQUID PLASTIC: CASE REPORT

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The objective is to report the surgical experience for one case with penetrating orbito-cranial combined injuries from high temperature plastic, we discuss the surgical key points and some announcements.

By imaging examination and physical examination, we found that the plastic foreign bodies were inserted into the patient's right eye socket, which passed across orbital medial penetrating orbital plate into the supraorbital fissure and anterior skull base. Using the right fronto-temporal joint approach, the intracranial wound track was fully exposed in operation. Due to the larger volume tip of foreign bodies which were fixed in the orbit and could not be removed directly by cranial or orbital department, intracranial foreign body could be only disconnected from the orbital plate first, and then a thorough debridement was done. The tissue spaces around the orbital foreign bodies were then separated out, and the residual plastic foreign bodies incarcerated in upper eyelid, intraorbital and outside the orbit were taken out. Finally, the reconstruction of the skull base was implemented by neurosurgery.

After joint surgery by neurosurgeon and ophthalmology, removal of orbital cranial foreign bodies, orbital-cranial wound debridement, and the reconstruction of the skull base were finished during the same period. The patient was cured through an operation with intact eye ball at the injury side.

The state of these penetrating orbito-cranial wounds is complicated, which will be difficult to handle and may directly endanger life. Methods of dealing with orbital cranial penetrating injury have their particularity. Based on the application of effective broad spectrum antibiotics, the situation of foreign bodies and the wounded, and their correlation with orbital or cranial injury should be clearly detected as early as possible. According to the traumatic condition, it is the key to take the appropriate surgical strategy for cure of this combined injury. Because of complex structure and wide range around the injury, the operation often needs multidisciplinary collaboration.

Key words
combined injury, cranium, high temperature plastic, orbit, penetrating injury, surgery

A1-02

THE INTRATHORACIC PRESSURE REGULATOR LOWERS INTRACRANIAL PRESSURE IN PATIENTS WITH ALTERED INTRACRANIAL ELASTANCE: A PILOT

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Intrathoracic pressure regulator (ITPR) is a noninvasive device designed to improve hemodynamics. Application of negative pressure during the expiratory phase of ventilation decreases intrathoracic pressure and enhances venous return. ITPR can potentially decrease intracranial pressure (ICP) and increase cerebral perfusion pressure (CPP) in brain-injured patients. We conducted an open-label study of the ITPR in patients with an ICP monitor and altered intracranial elastance.

Baseline hemodynamic variables and ICP were recorded prior to inserting one of the two ITPRs into the ventilator circuit based on a randomization scheme. Depending on the device, activation provided either -5 or -9 mmHg endotracheal tube pressure. Hemodynamic and ICP data were recorded sequentially every 2 minutes for 10 minutes. The first device was turned off for 10 minutes, removed and the second device was applied, and the procedure was repeated for the second device.

Ten patients were enrolled. Baseline ICP ranged from 12 to 38 mm Hg. With device application, a decrease in ICP was observed in 16 of 20 applications. During treatment with the -5 mmHg device, there was a mean maximal decrease of 3.3 mmHg in ICP (21.7 vs. 18.4 mm Hg, $p=0.003$), which was associated with an increase in CPP of 6.5 mmHg (58.2 vs. 64.7 mmHg, $p=0.019$). During treatment with the -9 mmHg device, there was a mean maximal decrease of 2.4 mmHg in ICP (21.1 vs. 18.7 mmHg, $p=0.044$), which was associated with an increase in CPP of 6.5 mmHg (59.2 vs. 65.7 mmHg, $p=0.001$).

This pilot study demonstrates that use of the ITPR in patients with altered intracranial elastance is feasible. This data strongly suggest that the ITPR may be used to rapidly lower ICP and increase CPP without apparent adverse effects. Additional studies will be needed to assess longitudinal changes in ICP when the device is in use and to delineate treatment parameters.

Key words
cerebral perfusion pressure, intrathoracic pressure regulator, negative intrathoracic pressure, traumatic brain injury

A1-03

EARLY AND LATE TRACHEOSTOMY AFTER DECOMPRESSIVE CRANIECTOMY FOR SEVERE TRAUMATIC BRAIN INJURY

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The purpose of the study was to retrospectively compare the early and late tracheostomy in terms of ventilator days, intensive care unit (ICU) days, pneumonia, and clinical outcomes in patients with a severe traumatic brain injury (TBI) who underwent a decompressive craniectomy.

Patients who had a TBI and a Glasgow coma scale (GCS) score ≤ 8, and were treated with a unilateral or bilateral decompressive craniectomy were enrolled. Between January 2006 and December 2008, 37 patients were enrolled in the retrospective study. Percutaneous tracheostomies were performed by trained residents. According to the timing of the tracheostomy, the subjects were classified as the early (≤ 7 days; $N=20$) or late group (>7 days; $N=17$).

The average time of the tracheostomy was 3.2 ± 1.4 days in the early group and 9.7 ± 0.9 days in the late group. There was no statistically significant difference between the early and late groups with respect to total days of mechanical ventilation, ICU stay, Glasgow outcome score (GOS), and pneumonia incidence. The duration of

antibiotic administration for the treatment of pneumonia was shorter in the early group ($p = 0.04$). Klebsiella species were the most common pathogens in both groups.

Early tracheostomy decreased the antibiotic period for the treatment of pneumonia in patients with severe TBI who underwent decompressive craniectomy. Early tracheostomy did not reduce total time of mechanical ventilation, ICU stay, pneumonia incidence, and GOS.

Key words
intensive care unit, tracheostomy, traumatic brain injury

A1-04

INFLAMMATION IN TRAUMATIC BRAIN INJURY WITH HEMORRHAGIC SHOCK

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Patients with traumatic brain injury (TBI) or hemorrhage shock (HS) frequently develop the systemic inflammation response syndrome (SIRS). SIRS is a primary risk factor associated with developing organ dysfunction and poor prognosis. TBI and HS are common injury components in multiply injured patients and often occur together. It is not clear how combined TBI and HS affect the pathogenesis of systemic inflammation. In this study, we developed a rat model of combined TBI/HS and quantified serum changes in damage associated molecular patterns that occurred due to TBI with or without HS. Subsequently, we quantified changes in liver AMPK as a surrogate for inflammation-mediated organ dysfunction.

TBI was induced in adult Sprague Dawley rats using controlled cortical impact (CCI) method. HS was induced by controlled hemorrhage via femoral artery to a mean arterial pressure of 40 mmHg (maintained 60 min). Mitochondrial DNA (mtDNA) fragments were measured by PCR and high-mobility group protein 1 (HMGB1) was measured using ELISA from 3 hours to 72 hours after injury. AMPK was measured from the liver after sacrifice using ELISA.

Severe ipsilateral cortical injury was observed 24 h after TBI, and the presence of HS did not affect the severity of injury. Serum levels of mtDNA gradually increased up to 72 hours after injury in TBI specimens. In TBI/HS specimens, significant increases in mtDNA occurred 3 hrs post injury and returned to baseline at 24 hours before a second significant increase at 72 hours post injury. Serum HMGB1 levels change in a pattern similar to those of mtDNA. Liver parenchymal AMPK levels were not affected in TBI specs and decreased 60% in TBI/HS specimens.

The present study established an animal model of TBI +/- HS in rats. The above results suggest that HS potentiates inflammation caused by TBI. In addition, remote organ energetic changes occurred in animals sustaining combined TBI/HS. More studies are needed to elucidate the inflammation pathways and develop potential agents to block this pathological process.

Key words
AMPK, hemorrhagic shock, HMGB1, mtDNA, TBI

A1-05

DEVELOPMENT OF A PORTABLE CEREBRAL MICRODIALYSIS PLATFORM FOR AUTOMATED INLINE MULTI-ANALYTE DETECTION SYSTEM

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An estimated 1.7 million traumatic brain injury (TBI) cases are reported every year in the United States with 15% of these being severe enough to require invasive monitoring. There is an urgent need for development of a bed-side, microdialysis system with in-built analyzer which will help in rapid and continuous monitoring of the state of health of a patient with severe TBI. The current state-of-the-art involves sample collection, labeling, storage and batch analysis that can take hours, if not days, which precludes results from being effectively used for clinical decision making. This protocol not only requires trained practitioners, but also is prone to errors in handling tiny amounts of dialysate. Moreover, current commercial instruments are limited to the analysis of small molecule metabolic biomarkers; these instruments do not detect large molecule biomarkers such as proteins. MD Analyzer™, being developed by SFC Fluidics, is an advancement over current microdialysis-based diagnostics for severe TBI, because all steps of the analysis will occur at bed side; clinically actionable results will be provided every 15 minutes for metabolic biomarkers, lactate (0–8 mmol/L), glutamate (1–400 μmol/L), pyruvate (0–250 μmol/L), and every hour for protein biomarker, S100B (20–200 ng/mL), detection. The first generation prototype described here integrates different innovative technologies like a non-mechanical electrochemical pumping system ePump®, Quickconnect™ fluidics coupling, electrochemical sensors for small molecule detection and a flow through Enzyme Linked Immunosorbent Assay (ELISA) for protein detection. This fully automated system moves the perfusate through a standard microdialysis probe, collects the dialysate and analyzes it in near-real time with little or no user intervention. Data presented will be detection of different concentration of biomarkers in spiked *artificial cerebrospinal fluid*. Availability of this nurse-friendly fully integrated system that automatically collects analyzes and reports the dynamic changes in concentrations of clinically relevant biomarkers will significantly ameliorate the patient care in Neurointensive Care Units (NICU).

Key words
ELISA, instrumentation, microdialysis, real-time detection, S100B

A1-06

VALIDATION OF THE IMPACT PROGNOSTIC MODELS

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Several prognostic models have been developed for traumatic brain injury (TBI) but have limited applicability due to development from small datasets. The International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) models, derived from several clinical trial datasets, were developed for prediction of mortality versus survival or unfavorable versus favorable outcome at 6-months post-injury. In order to confirm utility across centers, external validation is necessary. The purpose of this study was to evaluate the performance of three IMPACT models for prediction of 6-month post-injury mortality and dichotomized neurologic outcome (unfavorable/favorable) using data collected from a Level I trauma center registry. We analyzed admission data on 354 consecutive adult (≥ 16 years) patients that sustained blunt TBI with Glasgow Coma Scale sum score ≤ 12 (moderate or severe TBI). IMPACT model predictions of mortality (Extended Glasgow Outcome Scale [GOS-E] = 1) versus survival (GOS-E = 2-8) and unfavorable (GOS-E = 1–4) versus favorable outcome (GOS-E = 5–8) were compared to the actual observed classifications using logistic regression. The ability

of each model to correctly assign patients to groups was evaluated by calculating the area under the receiver operating characteristics curve (AUC). The IMPACT models performed with increasing accuracy in each more complex model. The ability to discriminate between mortality and survival was 0.85 for the Core model, 0.87 for the Extended model, and 0.87 for the Lab model in AUC analysis. The ability to discriminate between unfavorable and favorable outcomes was 0.84 for the Core model, 0.85 for the Extended model, and 0.87 for the Lab model in AUC analysis. The models were able to discriminate well between patients with mortality versus survival and unfavorable versus favorable outcome in all three IMPACT models in this non-trial dataset.

Key words
outcome measures, prognosis, prognostic model, traumatic brain injury

A1-07

MODULATION OF INFLAMMATORY CYTOKINE BALANCE BY SYMPATHETIC NERVOUS SYSTEM ACTIVATION AFTER TRAUMATIC BRAIN INJURY

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TBI elevates intracranial pressure and activates the sympathetic nervous system (SNS) with massive catecholamine secretion and modulation of neuroimmune networks. Hyperadrenergic activity is detrimental to the injured brain, amplifying secondary host inflammatory cascades. The extent to which the post-injury sympathetic surge contributes to pro-/anti-inflammatory cytokine dysregulation and impacts neurological outcome remains ill-defined. This study evaluated temporal changes in circulating cytokines in association with plasma epinephrine (E) and norepinephrine (NE) levels after TBI and interrelationships with neurological outcome. Isolated head-injury patients [$N = 194$; (mean ± SD) age 37 ± 18 y; 66% male] hospitalized with moderate (27%) to severe (73%) TBI, defined as a Glasgow Coma Scale (GCS) score of 8–10 or ≤ 8. Peripheral blood samples were drawn from TBI patients on admission, 6, 12 and 24-h post-injury; matching samples were collected from age-matched elective neurosurgical patients ($N = 15$) and healthy volunteers ($N = 15$). Plasma levels (pg/mL) of interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12, tumor necrosis factor (TNF)-α and interferon (IFN)-γ were quantified using high-density, ultra-sensitive MULTI-ARRAY® immunoassay; E and NE were measured by commercially available immunoassay (CatCombi). Neurological outcome was assessed at discharge and 6 months using Glasgow Outcome Scale. Mean (±SEM) values of E (3.1 ± 2.1) and NE (280 ± 68) were within reported normal ranges for healthy controls. Relative to healthy controls, neurosurgical patients showed moderately elevated levels of E (135 ± 19) and NE (855 ± 281). By comparison, severe TBI patients exhibited highly elevated E values, which peaked on admission (666 ± 189) and gradually decreased over time. Similarly, NE was markedly higher at all time-points, with max increases at 12 h (10982.8 ± 7310). TNF-α and IL-10 were differentially regulated in moderate and severe TBI relative to controls. These results demonstrate significant SNS activation after TBI, which correlates with inflammatory cytokine profiles and neurological outcome.

Key words
catecholamines, cytokines, IL-10, TNF

A1-08

MULTIMODALITY MONITORING OF PLATELET FUNCTION IN TRAUMATIC BRAIN INJURY PATIENTS WITH TRAUMA INDUCED COAGULOPATHY

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Coagulopathy occurs in 33% of traumatic brain injury (TBI) patients during their hospital course. Platelet (PLT) function is a key mediator of hemostasis; however, it remains poorly described in trauma induced coagulopathy (TIC) in TBI patients. As part of a prospective observational polytrauma study, PLT function in TBI patients with TIC was characterizes upon emergency department (ED) admission. A total of 99 trauma patients were enrolled between 2011 and 2013. Platelet function was assessed by thromboelastography (TEG) with PLT mapping; Hemodyne (HAS); aggregometry; calibrated automated thrombography (CAT); and flow cytometry. TIC was defined as INR ≥ 1.4. Patients were divided into 2 groups based on presence or absence of TIC and compared to a group of healthy volunteers. Of the 27 TBI patients identified, 41% had TIC. TIC patients had significantly higher injury severity scores, lower base excess and Hb consistent with hemorrhagic shock, and higher inflammatory biomarker (IL-6) levels compared to those without TIC ($p < 0.01$). TBI patients without coagulopathy showed a pro-coagulation profile (higher platelet contractile force (PFC) and clot elastic modulus (CEM), and shorter R-time versus controls ($p < 0.05$), while TIC patients showed lower fibrinogen levels with a decrease in clot strength (lower CEM and MA), and lower plasma peak thrombin generation (C-max)($p < 0.05$). Platelet mapping found patients without coagulopathy presented with significant inhibition of PLT ADP-mediated responsiveness compared to controls (83% vs 53%, $p < 0.01$), while responsiveness was further reduced with TIC (96%, $p < 0.01$). TBI polytrauma patients with TIC upon ED admit present with impaired platelet function, lower fibrinogen, lower plasma peak thrombin generation, and elevated IL-6 which may increase the risk of uncontrollable hemorrhage. Multimodality monitoring of coagulation, including platelet function, contributes to the understanding of hemostasis.

Key words
coagulation, platelet function

A1-09

TRENDS IN EMERGENCY DEPARTMENT TREATMENT OF SPORT-RELATED TRAUMATIC BRAIN INJURY, 2006–2011

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Traumatic brain injury (TBI) in sports has received substantial attention in recent years, leading sport and government officials to implement policies aimed at preventing such injuries or reducing their severity. We sought to identify trends associated with sports-related TBI in Emergency Departments (ED) nationwide from 2006–2011.

TBI data from the Nationwide Emergency Department Sample were gathered and sport-related injuries were identified by E-code. Patient characteristics were compared using chi-squared tests and odds of inpatient admission were calculated using logistic regression.

A total of 106,217 sport-related TBIs occurred over a period from 2006–2011. Of these, 70,509 (66.4%) were among middle school- or high school-aged adolescents (age 12–18). Overall, ED presentation with sports-related TBI increased 77.5% from 53,058 in 2006 to 94,181 in 2011. The number of patients admitted to inpatient care increased by 8.0%, from 2,850 to 3,078, over the same period, however the actual proportion of ED patients admitted to inpatient care decreased from 5.4% in 2006 to 3.3% in 2011. Across the study period, patients in the Midwest/West were proportionally more likely to be admitted than those in the East/South.

Increased ED presentation with sport-related TBI is cause for concern, especially among school-age adolescents. Falling admission rates suggest that the rise in ED presentations may be driven by increased TBI awareness rather than by increasing TBI incidence. While additional research is warranted, it is clear that the prevention of sport-related TBI, especially among adolescents, must be addressed.

Key words
emergency department, epidemiology, sports-related, TBI

A1-10

ACUTE CARE CLINICAL INDICATORS ASSOCIATED WITH DISCHARGE OUTCOMES IN CHILDREN WITH SEVERE TRAUMATIC BRAIN INJURY

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We tested the relationship between severe pediatric traumatic brain injury (TBI) guideline indicators during the first 72 hours after hospital admission and discharge outcomes.

Records of children ≤ 17 years with severe TBI were abstracted at 5 pediatric trauma centers. Total percent adherence to the clinical indicators across all treatment locations (pre-hospital [PH], emergency department [ED], operating room [OR], and intensive care unit [ICU] were determined. Main outcomes were discharge survival and Glascow outcome scale (GOS) score. Total adherence rate ranged from 68–78%. Clinical indicators of adherence were associated with survival (aHR 0.94; 95% CI 0.91, 0.96). Three indicators were associated with survival: absence of PH hypoxia (aHR 0.20; 95% CI 0.08, 0.46), early ICU start of nutrition (aHR 0.06; 95% CI 0.01, 0.26), and ICU $paCO_2 < 30$ mm Hg in the absence of radiographic or clinical signs of cerebral herniation (aHR 0.22; 95% CI 0.06, 0.8). Clinical indicators of adherence were associated with favorable GOS among survivors (aHR 0.99; 95% CI 0.98, 0.99). Three indicators were associated with favorable discharge GOS: all OR CPP > 40 mm Hg (aRR 0.64; 95% CI 0.55, 0.75), all ICU CPP > 40 mm Hg (aRR 0.74; 95% CI 0.63, 0.87), and no surgery (any type); aRR 0.72; 95% CI 0.53, 0.97).

Acute care clinical indicators of adherence to the Pediatric Guidelines were associated with significantly higher discharge survival and improved discharge GOS. Some indicators were protective, regardless of treatment location.

Key words
evidence-based guidelines, outcomes, pediatric, traumatic brain injury

A1-11

PLASMA AND CEREBROSPINAL FLUID ERYTHROPOIETIN CONCENTRATIONS FOLLOWING ERYTHROPOIETIN ADMINISTRATION IN TRAUMATIC BRAIN INJURY

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The objective is to examine erythropoietin (EPO) dynamics in plasma and CSF following erythropoietin administration in patients with traumatic brain injury (TBI).

As part of a study of transfusion threshold and epoetin alfa administration (500 IU/kg EPO [Epogen®, Amgen, Inc., Thousand Oaks, CA]) in TBI, EPO concentrations were measured by ELISA in plasma and CSF at 6, 12, 24, 48, 72 and 96 hours after injury. Patients (N = 200) were randomized to placebo (N = 98), single dose EPO (N = 64) or three doses of EPO (N = 38) given 24 hours apart started within 6 hours of injury.

Before treatment, the median plasma EPO levels were 15.7 (interquartile range [IQR] = 40.3) mIU/ml (normal range 4–27 mIU/ml). In the placebo group, the median plasma EPO levels gradually increased over time, peaking at 111.6 (IQR = 161.5) mIU/ml at 48 hours after injury. In the patients receiving EPO, the median plasma levels peaked at 1,745.0 (IQR = 770.5) mIU/ml at 12 hours after injury. These plasma levels of EPO were sustained in the patients receiving three doses compared to those receiving a single dose.

Prior to the initial dose, CSF EPO was undetectable in most patients. In patients receiving EPO, the median CSF levels increased to 11.8 (IQR = 64.7) mIU/ml at 12 hours after injury and peaked at 18 hours, and remained elevated above baseline values through 48 hours. In the placebo group, EPO peaked at 48 and 72 hours.

EPO administration results in a sustained rise of plasma and CSF EPO levels. CSF levels are approximately 1% of plasma levels indicating small but definite CNS penetration. There is an endogenous EPO response in the placebo group consisting of a gradual increase in both plasma and CSF that peaks 4 days after injury. (Supported by National Institute of Neurological Disorders and Stroke P01-NS38660).

Key words
anemia, cerebrospinal fluid, erythropoietin, pharmacokinetics

A1-12

WHAT WILL YOU SEE IN INTRACRANIAL PRESSURE WAVEFORM ANALYSIS?

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Intracranial pressure (ICP) is monitored commonly in the severe traumatic brain injury. However, we only know the facts from the value of the mean ICP whether ICP is high or low. It does not reflect

various brain pathological conditions correctly. Therefore, we take a closer look at the waveform of ICP in the several pathologic condition. The data of ICP waveform (ICPWF) was monitored in water intoxicated rat model and continuous infusion model using Biopac MP150 system (BIOPAC USAW). On cite of clinical, the ICP data of 16 trauma patients and 9 cerebrovascular disease patients in whom ICPWF was monitored continuously by ICP express® (Codman USA). Differential ICPWF was calculated using LabChart® Software (AD instrument, USA).

Continuous monitoring of ICPWF showed clarify waveform change and the change over time of the pressure. Single ICPWF was expressed as 3-phase wave (P1, P2, P3), 3-phase wave was reflected as U1, U2, U3 in the differential ICPWF. In accordance with increased ICP Continuous infusion as interstitial edema model demonstrates high amplitude ICPWF and elevated P1, U1. In contrast, water intoxication as cellular edema model showed low amplitude ICPWF, numerous b wave and U2 elevation during high ICP. Also in clinical cases, ICPWF were divided roughly into two groups. One group showed the increased U1, there was a tendency to include increased ICP patients with a massive hematoma. Another elevated U2 group tended to be more common in cases of severe traumatic brain injury and cerebral infarction patients.

Although mean ICP was the same degree, the difference of ICPWFs was observed in different pathogenic brain condition: extracellular edema and intracellular edema. It suggests ICP waveform analysis will be more valuable for assessment of brain's pathological condition like several type of brain edema.

Key words
differentiated intracranial pressure waveform

A1-13

FACTORS ASSOCIATED WITH CLINICIAN ADHERENCE TO PEDIATRIC TRAUMATIC BRAIN INJURY GUIDELINES: A QUALITATIVE STUDY

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Evidence-based medicine may be influenced by provider beliefs and competencies, professional norms, and managerial support. This study assessed factors specific to adherence to the Brain Trauma Foundation pediatric traumatic brain injury (TBI) guidelines. We conducted nineteen focus groups with physicians (n = 54) and nurses (n = 74) who treat pediatric patients with TBI at six pediatric-trauma centers (Chicago, Columbus, Los Angeles, Pittsburgh, and Seattle). Sessions were transcribed and examined using content analysis to identify themes related to guideline adherence. Barriers and facilitators of clinical adherence to the pediatric TBI guidelines were identified. Three domains emerged: 1) the implementation and agreement of institutional protocols with the guidelines, 2) inter- and intra-department communication and decision making, and 3) and perceived guideline credibility and practicality. Dissemination and accountability structures used to implement institutional protocols, and the level of agreement between protocols and TBI guidelines influenced clinical decisions. Communication and decision making were affected by the quality of platforms for inter- and intra-department communication and the establishment of common treatment goals. Clinicians reported value in clear care pathways, identified and accessible decision makers, departmental liaisons, and provider consensus of guideline application in local practice. Guideline credibility was rooted in the perceived strength of the evidence, and alignment with clinical experience and training. Practicality was determined by applicability to the patient. Identifying remediable provider and organizational factors that impact guideline adherence will inform changes to pediatric TBI care pathways and the development of future TBI treatment recommendations.

Key words
adherence, guidelines, qualitative, TBI

A1-14

COMPARATIVE STUDY OF OUTCOME MEASURES AND ANALYSIS METHODS FOR TRAUMATIC BRAIN INJURY TRIALS

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Batteries of functional and cognitive measures have been proposed as alternatives to the Extended Glasgow Outcome Scale (GOSE) as the primary outcome for traumatic brain injury (TBI) trials. We conducted a study to compare GOSE and a battery of functional and cognitive measures.

Several analytic methods were evaluated for each outcome. Using data from a randomized trial, we simulated multiple treatment effects (0, 5, 7.5, and 10 percentage point improvement in favorable outcome on GOSE and a corresponding deficit reduction for other measures) across multiple outcome measures. Patients with complete data (n = 331) were sampled with replacement (bootstrapping) to generate 10,000 samples for each treatment effect (n = 400 patients/group). We calculated the percentage of samples where the null hypothesis was rejected to estimate the power for each outcome with a suite of analytic techniques. Type-I error was estimated by analyzing the simulation with 0% treatment effect.

All analytic techniques had appropriate rates of Type-I error ($\leq 5\%$). Accounting for baseline prognosis, either by using sliding dichotomy for GOSE or using regression-based methods substantially increased the power over the corresponding analysis without accounting for prognosis. The highest power was obtained using multivariate proportional odds regression to analyze GOSE or using regression-based adjusted analysis of the battery of functional and cognitive measures, assuming equal treatment effect across all components. Analyzing GOSE using the fixed dichotomy provided the lowest power for both unadjusted and regression-adjusted analyses.

Our findings are limited to situations where the assumption of equal treatment effect across all measures is satisfied. This may not be true in an actual clinical trial.

Accounting for baseline prognosis is critical to attaining high power in phase-III TBI trials. The choice of primary outcome for future trials should be guided by the domain of brain function an intervention is likely to impact and the feasibility of data collection.

Key words
clinical trial, Glasgow Outcome Scale, outcome measures, research design, statistical data analysis, traumatic brain injury

A1-15

HIGH INCIDENCE OF DELAYED SEIZURES IN SEVERE TBI PATIENTS

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After Traumatic Brain Injury (TBI) early seizure susceptibility is well recognized but human studies of incidence and progression of epileptogenesis are limited. Animal models have demonstrated that MRI biomarkers may predict seizure susceptibility after TBI. In this study we sought to determine the incidence and potential predictors for the development of delayed (beyond 7 days) seizures in humans.

Forty-six patients with severe TBI, enrolled from 2001–2011, were contacted 2–10 years post-injury to evaluate incidence of seizures. 37 patients had acute volumetric T1-weighted MRIs. Principal components analysis (HCPC) of acute injury factors to determine predictability of delayed seizures was performed using the LONI pipeline, featuring anatomic MRI evaluation of area, volume, shape index, average, curvature, curvedness, and fractal dimension.

Mean age at injury was 36.9 ± 17.3 years (9 females and 37 males). Mean GCS was 5.5 ± 3.3. CT lesions included 23 (50%) contusional and 18 (39.1%) DAI plus contusion. 25/46 (52.2%) developed seizures after TBI. Seizures developed 0–7 days post-injury in 12 patients (26.1%), 7–30 days post-injury in 6 patients (13.0%) and after one month post-injury in 7 patients (15.2%). Of the 12 patients that developed seizures acutely, 4 (8.7%) subsequently had seizures after 30 days post-injury. Multivariate analysis demonstrated GCS, acute neurosurgical intervention, and acute seizures independently predicted subacute seizures. Thalamic shape measurements, computed from acute MRIs in an automated hierarchical clustering using HCPC, predicted subacute seizures with limited accuracy of 0.67. A subsequent global analysis predicted subacute seizures with 0.76 accuracy.

Our results indicate a high incidence of seizures after severe TBI both acutely and subacutely. Potential early predictors of subacute seizures include GCS, surgical intervention, and acute seizures. Acute morphometric features of injury did not accurately predict subacute seizures. Subacute seizures occur for reasons that are not yet clear.

Key words
magnetic resonance imaging, seizure, traumatic brain injury

A1-16

DECOMPRESSIVE CRANIECTOMY IN TRAUMATIC BRAIN INJURY: DETERMINING OPTIMAL FLAP SIZE FOR BETTER INTRACRANIAL PRESSURE CONTROL

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While controversial, the use of decompressive craniectomy (DC) for the treatment of refractory ICP remains widely used in the neurotrauma setting. Indeed, while the *DECRA* trial reports DC may be associated with more unfavorable outcomes, our institution, similarly to the ongoing *RESCUEicp* trial, recommends large fronto-temporo-parietal DC. Furthermore, the literature shows great discrepancies as to what constitutes optimal craniectomy size, with varying methods for reporting and measuring flap size, usual guideline being a minimal diameter of 12 cm. Our study aims to identify optimal bone flap size and clarify the way it is reported. All the cases of severe TBI requiring DC at the Montreal General Hospital over the last ten years were retrospectively reviewed and we identified thirty cases that required such a procedure for pure cerebral swelling. We correlated the craniectomy size (diameter, circumference, surface area) to different clinical variables (hospital and ICU stays, GOS, ICP control, hypertonic infusion). Thirty patients with severe TBI were identified (mean age of 30 ± 2 years, presenting GCS of 7.5 ± 0.4), all requiring DC at 63 ± 9 hours after trauma for refractory ICP. Eighty three percent had an initial Marshall CT-score of 3. Better ICP control was achieved for DCs with a ratio of flap circumference over skull hemicircumference of more than 65% (over 96 hours post-operatively, $p < 0.05$). A tendency towards less post-operative hypertonic infusion was also found (9.8 ± 1.7 L vs 6.1 ± 1.9L; $p = 0.11$). In our study, only 40% of DC diameter over 12 cm (usual guideline) made it to the larger circumference ratio group, hence achieving better ICP control. According to our results, this 12 cm diameter threshold might be insufficient. Furthermore, it is impossible to measure it preoperatively since it is a post-operative measurement. By standardizing craniectomy flap measurement, we hope to provide an easy intraoperative guideline (flap circumference) in order to ensure an adequate size craniectomy and potentially better outcome of patients through better ICP control.

Key words
bone flap size, decompressive craniectomy, fronto-temporo-parietal craniectomy, severe traumatic brain injury

A1-17

BRAIN TISSUE OXYGENATION AND 3, 6-MONTH NEUROLOGICAL OUTCOME IN SEVERE TRAUMATIC BRAIN INJURY

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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 3 and 6-month outcome in adult sTBI.

Under an approved IRB protocol, $PbtO_2$ data were prospectively collected on sTBI patients (Glasgow Coma Scale (GCS) score < 9) during the acute 5 days following injury. Glasgow Outcome Scale (GOS) score, a measurement of neurologic outcome, was assessed at 3 and 6-months from injury and dicotomized into poor (GOS 1-3) and favorable outcome (GOS 4-5). Statistical analyses were performed using a logistic regression model controlling for age and initial severity of injury.

258 adult, sTBI patients, mean age($\pm$SD) was 38 ($\pm$17) years, with 69% male and a median GCS of 6 with 3 and 6-month outcome were included. ICU management included ICP management per Guidelines of sTBI Management; however, $PbtO_2$ was not treated, just monitored. Post-trauma day (PTD) 2 $PbtO_2$ data was chosen for analysis to avoid insertional microtrauma and minimize variability of values seen within the first 24 hours. Receiver operating characteristic curve analysis resulted in cut-off values: minimum $PbtO_2 < 16.03$ and maximum < 37.15, significant for poor 3-month neurological outcome [OR 2.46 (1.29, 4.68), $p = .004$, OR 2.71 (1.37, 5.33), $p = .006$ respectively]. There was no significance for 6-month neurological outcome at these same cutoffs; however, PTD2 $PbtO_2$ values in combination for minimum < 18.3, maximum < 37.2 and average < 24.3 had a OR 2.02 (1.11, 3.67), $p = .021$.

Monitoring of $PbtO_2$ in the adult sTBI population may be predictive of 3 month neurological outcome and providing a target cohort for early rehabilitation efforts. Additional studies are needed to assess the effectiveness of treating $PbtO_2$ values.

Key words
brain oxygenation, clinical, neurological outcome

A1-18

INFLUENCE OF SYSTEMIC GLUCOSE ON KETOGENIC METABOLITES

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Maintaining blood glucose below hyperglycemic (200 mg/dL) and above hypoglycemic levels (80 mg/dL) is a critical aspect of post-TBI care. Research on modulating patients' blood glucose to low glycemic ranges (80–110 mg/dL) has produced conflicting results regarding outcome. The objective of this study is to investigate metabolic changes beyond systemic glucose under low glycemia. Arterial and jugular venous blood plasma and CSF were repeatedly collected from fifteen patients following severe head injuries (3 females, age 39 ± 16, GCS^{ER} 6.8 ± 4.2). Clinical glucose measurements approximated periods of low glycemia (≤ 115 mg/dL) and of moderate glycemia (>115 mg/dL) during the first ten days following injury; all 15 patients included had biofluids collected during both periods. Biofluid metabolite concentrations were determined by NMR spectroscopy. Blood glucose decreased at low glycemic levels (103 ± 19 from 145 ± 21 mg/dL). Systemic ketone bodies were increased at low glycemic levels (β-hydroxybutyrate (β-HB) 128 ± 130 to 222 ± 235 μM; acetoacetic acid(AcAc) 66 ± 85 to 115 ± 152 μM) but a robust, dependent yuen test did not reveal statistical significance. We used mixed effects models (MEM) to account for repeated collection/measurement and to investigate the effect of low glycemia on biofluid metabolites and their relationship between biofluids. MEM of AcAc concentration with the fixed effects of glycemic level, post-injury hour (PIH), biofluid compartment, and the interaction between glycemic level and PIH revealed a significant increase in AcAc at low glycemic levels (202 ± 41 μM, $p<0.001$), a significant decrease in CSF AcAc compared to plasma (-77 ± 16 μM, $p<0.001$), and a significant interaction between glycemic level and PIH (-1.2 ± 0.4 μM, $p=0.002$). β-HB concentration modeling with the fixed effects of glycemic level, PIH, biofluid compartment, and the interactions of glycemic level with PIH and with biofluid location revealed a significant increase in β-HB at low glycemic levels (438 ± 98 μM, $p<0.001$) and a significant interaction between glycemic level and PIH (-2.4 ± 0.7 μM, $p<0.001$). These results suggest the body increases ketone production at low glycemic levels and does so to a greater degree at early PIH.

Key words
glycemia, ketones, metabolite

A1-19

THE INDO-US COLLABORATIVE HEAD INJURY AND ADHERENCE TO GUIDELINES (CHIRAG) PROJECT: OUTCOMES AND FEASIBILITY

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Traumatic brain injury (TBI) is a major public health problem in both the U.S. and India. The CHIRAG project examines the relationship between adherence to the 2007 Brain Trauma Foundation Guidelines and outcomes in severe TBI patients at Harborview Medical Center (HMC, Seattle) and JPN Apex Trauma Center (JPN, New Delhi). Here, we report results on clinical characteristics and both short-term and long-term outcomes at JPN, as well as project feasibility.

After separate local IRB approvals were obtained, we conducted a prospective study with one-year patient follow-up at JPN between 2012–2014 to assess guideline adherence and outcomes after severe TBI; for comparison, similar data was collected retrospectively from severe TBI patients admitted to HMC. Inclusion criteria were: age ≥ 18 years, admission Glasgow Coma Scale (GCS) score <9 and head Abbreviated Injury Score (AIS) ≥ 3, intubated in intensive care unit (ICU) ≥ 48 hours and no CPR prior to admission.

At JPN, 200 patients were enrolled prospectively over two years. Table 1 shows the clinical characteristics of enrolled patients, both at HMC and JPN. Overall, JPN patients were younger and had less polytrauma. Compared to local HMC mortality rates, discharge mortality was similar; however, post-discharge outcomes (including both mortality and neurologic improvement) appeared worse in the JPN group.

Success with the CHIRAG project suggests that joint Indo-US TBI studies are feasible. Descriptive analysis suggests some baseline differences in clinical characteristics of severe TBI patients pertaining to extracranial injury and injury severity. While discharge mortality was similar between HMC and JPN, post-discharge outcomes appeared worse in the JPN group. Future research should address post-hospital discharge factors that may improve outcomes in this population.

Key words
global health, outcomes, TBI

A1-20

NEUROPHYSIOLOGICAL TESTING FOR LONG-TERM PROGNOSIS IN SEVERE TRAUMATIC BRAIN INJURED PATIENTS

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Prognostication in the acute phase of severe traumatic brain injury (TBI) remains difficult. Somatosensory evoked potentials (SSEPs) as a neurophysiologic testing modality may provide a reliable objective mechanism for TBI prognostication. Under an IRB-approved protocol, prospective clinical and outcome data were collected from all severe TBI patients (Glasgow Coma Score ≤ 8) admitted to UPMC between 2006–2011. SEP recording was performed on post-trauma day 5. N9, N13, P14, N20, and P30 latencies are measured; central conduction time (CCT) is defined as the delay between the P14 peak recorded at the C-2 electrode and the N20 peak recorded at the somatosensory cortex. Peak-to-peak amplitudes measured are of N20/P30 using Fz reference. Criterion for pathologic SEP event was defined as either the reduction of the N20 amplitude below 50% of baseline or the increase of latency between P14 and N20 by 10%.

SEPs were graded as bilaterally absent, unilateral absence, bilateral delay > 23ms, unilateral delay with normal, and bilateral normal latency. Functional outcome was prospectively collected at 12-month follow-up, and included neurologic status and mortality as assessed by Glasgow Outcome Scale (GOS). 134 patients were available for analysis. Median GCS was 6 (IQR 2), while median radiographic injury was a Marshall score 3 (IQR 2). Mean age was 38 ± 16. Univariable analysis of SEP demonstrated significant ordinal prediction of outcome according to GOS; for every increase in SEP grade, there was an increased chance of favorable outcome [OR = 1.59 (1.3–1.9), $p < 0.001$]. SEP demonstrating bilateral delayed latencies, unilateral delayed latencies, or normal SEP responses significantly differentiated favorable vs. unfavorable outcome (OR 5.78, 95%CI 2.43-13.7, $p < 0.001$). These findings remained significant regardless of age, admission GCS, or radiographic injury severity ($p > 0.59$ respectively). Diagnostic neurophysiological testing in the acute phase of severe TBI has shown to be a significant predictor of long-term outcome.

Key words
clinical, imaging, neurophysiology

A1-21

LESSONS IN CRITICAL CARE RESEARCH FROM A GLOBAL PHASE 3 TRIAL OF PROGESTERONE IN PATIENTS WITH SEVERE TBI

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BHR-100 progesterone i.v. infusion was studied as a potential neuroprotectant for severe TBI. The SyNAPSe Phase 3 placebo-controlled randomized clinical trial was conducted in 21 countries on patients with severe TBI (Glasgow Coma Scale 3–8). The trial has been completed, overcoming numerous challenges in clinical trial research in the critical care environment.

Sites were selected based on patient potential and standardized care according to Brain Trauma Foundation or equivalent treatment guidelines. Centralized review of CT scans, Glasgow Outcome Scores (GOS), and protocol compliance was conducted. Subjects required proxy consent to enter the study and were randomized in a 1:1 ratio to BHR-100 or placebo. The study drug infusion must have been initiated within 8 hours of brain injury, and administered for 120 continuous hours. All study procedures were required to be completed in the context of not interfering with the patients' medical care. Patient follow up continued to 6-months post-injury, or death if earlier.

Nearly 1200 subjects were randomized in 36 months. Most sites were able to overcome challenges of the 8-hr treatment window and enroll at least one patient. Successful sites had organized study teams and adequate resources, with at least one study 'champion'. Training or experience in emergency consent was essential, as well as thorough knowledge of all study assessments to ensure protocol compliance and data quality. Rigorous follow up and site and patient support was needed to collect the primary endpoint (GOS). The sponsor oversaw three CROs, multiple central services, and over 150 centers to conduct the trial.

Although bench-top researchers aim for eventual confirmation in a Phase 3 trial, conducting such a trial involves numerous challenges from an organizational as well as a participating site perspective. The SyNAPSe trial was completed and provides useful lessons for researchers planning future TBI or other critical care trials.

Key words
critical care research, SyNAPSe trial

A1-22

TREATMENT OF REFRACTORY INTRACRANIAL HYPERTENSION IN PATIENTS WITH TRAUMATIC INTRACRANIAL USING DECOMPRESSIVE CRANIECTOMY

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We compared the effect of early decompressive craniectomy (< 24 h) with that of non-operative treatment on the outcome of patients with refractory intracranial hypertension following severe traumatic brain injury.

A retrospective review was conducted of 24 consecutive patients who presented between 2010 and 2013 with refractory intracranial hypertension following isolated severe head injury with intracranial hematomas. Early decompressive craniectomy after hematoma removal (mean time from injury: 6.2 ± 3.2 h) was carried out in 12 patients (mean age: 35.3 ± 5.4 years), whereas 12 patients (mean age: 38.4 ± 3.1 years) were underwent only hematoma removal without decompressive craniectomy. In all patients treatment included sedation, paralysis, and IV mannitol under ICP monitoring. In the early decompressive craniectomy group 3 patients had EVD insertion and 5 had hypothermia. In the non-decompressive treatment group 4 patients had EVD insertion and 3 had hypothermia. The Glasgow Outcome Scale at follow-up was used as outcome measure.

All patients in the early decompressive craniectomy group survived; 3 patients scored 5, 5 patients scored 3 and 4 patients scored 4 on the GOS. In the non- decompressive treatment group 3 patients died, 2 patients scored 5, 3 patients scored 4 and 4 patient scored 2 on the GOS.

Early decompressive craniectomy, employed prior to the onset of irreversible ischemic changes, may be an effective method of treating the secondary deterioration from refractory intracranial hypertension following severe head injury with intracranial hematomas.

Key words
craniectomy, hematoma, intracranial hypertension

A2-01

MONITORING MILD TRAUMATIC BRAIN INJURY WITH POLARIZATION-SENSITIVE OPTICAL COHERENCE TOMOGRAPHY

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Mild traumatic brain injury (mTBI) may lead to disorientation and impaired consciousness and other neurological and cognitive sequelae. However, imaging diagnosis of mTBI is challenging. Since mTBI is diffuse, it is common for typical neuroimaging (CT and MRI scans) to show no evidence of injury. While it is clear that mTBI can lead to white matter damage, standard imaging techniques are poor at detecting mild injury. Therefore, in this study, we employed polarization-sensitive optical coherence tomography (PS-OCT) to detect continuous changes in tissue structure within the brain in a mouse model of mTBI. PS-OCT is capable of quantifying tissue birefringence, a phenomenon caused by highly organized tissue architecture such as myelin, by imaging the sample with two orthogonal polarization states. Using PS-OCT we observed a loss of birefringence within 30 minutes of impact. Furthermore, we correlated this decrease

through immunohistochemical (IHC) analysis of myelin basic protein (MBP) and neurofilament (NF200) and observed a down-regulation of MBP and NF200 as early as 2 hours post-injury. Our results demonstrate proof-of-concept of optical biomarker identification after mTBI and suggest PS-OCT as a promising diagnostic method for detecting changes in tissue dynamics in the clinical setting.

Key words
meylin, mild traumatic brain injury, neurofilament, optical coherence tomography

A2-02

WHITE MATTER INJURY IN A RODENT MODEL OF BLAST INJURY

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Exposure to explosive blast devices accounts for almost two thirds of the casualties substained by the US military in Iraqi and Afghanistan. The mechanism of primary blast injury to the central nervous system is less well characterized. This study aims to investigate the effect of a low level blast exposure on white matter injury in an experimental rodent model of blast exposure.

Briefly, male Sprague Dawley rats were exposed to a single blast at ~180kPa. The animal subjects were evaluated on the 5-choice serial reaction time and subjected to longitudinal diffuse tensor imaging (DTI). In addition, TUNEL assay for apoptotic cells and black gold myelin immunostaining was carried out on brain slices at −3.8 mm bregma at stipulated post-blast sacrifice timepoints (Day 1, 3, 5, 14, 28 post-blast).

There was an increase in TUNEL-positive apoptotic cells in the corpus callosum from 24 h to 1 month post-injury after blast. Furthermore, fractional anisotropy (FA) of the corpus callosum using DTI was found to be suppressed after low blast injury with recovery at 28 days. This suggests that the white fibre tracts are affected transiently after low blast injury. Furthermore, demyelination was also observed at the thalamus region using the Black-Gold staining. This disrupted myelination of the thalamus is corresponded by a transient decrease in substained attention in the 5CSRTT test from 3–6 days post-injury. Further investigations into the thalamus post-blast can be made to evaluate the role of the thalamus in funcational outcome post-blast.

Key words
blast injury, diffuse tensor imaging, fractional anisotropy, rodent model

A2-03

USING PET TO DETECT CHANGES IN BRAIN BLOOD FLOW AND METABOLISM AFTER CONTROLLED CORTICAL IMPACT IN MICE

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The use of PET imaging for translational research with rodent models of traumatic brain injury (TBI) is still a nascent field. To date, no PET studies have been conducted with the controlled cortical impact (CCI) model of TBI. We sought to determine the feasibility of [^{64}Cu]PTSM and [^{18}F]FDG PET for detecting changes in blood flow and metabolism in the CCI model in mice. Twenty-four male C57BL/6 mice (22.2 ± 1.59 g) received either a CCI to the left parietal cortex ($n = 14$) or a sham surgery (SHM; craniotomy but no impact; $n = 10$). Each animal received one anatomic MRI and one PET scan one week after surgery. Five SHM and 7 CCI animals received [^{18}F]FDG (glucose utilization); 5 SHM and 7 CCI received [^{64}Cu]PTSM (blood flow). Tracers were administered via tail vein while animals were awake and lightly restrained. Average doses for [^{18}F]FDG and [^{64}Cu]PTSM were 0.28 ± 0.02 and 0.12 ± 0.02 mCi, respectively. Average standardized uptake values (SUV) data were extracted from regions of interest (ROIs) that included bilateral parietal cortex, hippocampus, thalamus, and caudate. Paired *t*-tests were used for within-group comparisons of SUV between left and right ROIs. In TBI mice, [^{64}Cu]PTSM SUV was significantly lower in left parietal cortex (CCI lesion) relative to the non-lesioned side (-13%; $p < 0.005$). No craniotomy effects were detected in SHM. In TBI mice, [^{18}F]FDG SUV was significantly lower in the left parietal cortex (-14%, $p < 0.02$) and left hippocampus (-12%, $p < 0.03$) relative to the right side. In SHM mice, [^{18}F]FDG SUV was lower in the left hippocampus (-9%, $p < 0.02$); higher SUV was found in left thalamus (12%; $p < 0.03$). Standard deviations from the [^{18}F]FDG SHM group were twice that of the TBI group, indicating that larger sample sizes (> 5) are needed to reduce variance. Both [^{64}Cu]PTSM and [^{18}F]FDG show promise for monitoring acute and longitudinal effects of CCI on brain metabolism and blood flow.

Key words
blood flow, controlled cortical impact, glucose metabolism, mouse, positron emission tomography

A2-04

ACUTE AND 1 YEAR FOLLOW-UP MRI OF TRAUMATIC HEMORRHAGIC BRAIN LESIONS AFTER MODERATE/SEVERE PEDIATRIC TBI

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We present findings on acute and 1 year follow-up of hemorrhagic brain injury in pediatric TBI patients, studied with MRI susceptibility-weighted imaging (SWI).

Pediatric patients (4 to 18 y), with moderate/severe TBI (GCS score < 13 or hemorrhagic intracranial injury on CT) underwent MRI (3T), acutely (6–17 d), and at 1 year post injury. Number/volume of hemorrhagic lesions were compared with initial GCS and at the 2 time points.

Fifty-two children (38M/14F, mean age 12.3 years), were injured in vehicle/bike accidents (31), falls (12), sports-related injuries (7), or assaulted (1). Lesions numbered from 0–977/patient, and hemorrhagic volume ranged from 0–135 cc/patient. Extent of hemorrhages negatively correlated with initial GCS. Significant differences in hemorrhages were seen between GCS groups. Ten patients (GCS of 6–15) had no lesions, whereas 13/18 patients with GCS of 15 had lesions. Most lesions (80% of total number, 87% of total volume) occurred in the cerebral cortex and subcortical white matter. Frontal lobe lesions were most frequent (34% of total number, 65% of total volume), followed by temporal lobe lesions (29% of total number, 17% of total volume). Only 1 patient (with minimal lesions) showed 100% resolution at 1 year. In the remaining patients, the degree of reduction in

lesion number averaged 49% (range 0–81%) and the reduction in volume averaged 50% (range 0–89%). For brain subregions, greatest improvement (65% in number, 62% in volume) occurred in deep brain structures (CC, BG, THAL, IC). 46% of patients retained >50% of the initial lesion number and 37% retained >50% of the initial hemorrhagic volume.

Most traumatic hemorrhagic lesions occur in the cortex and subcortical white matter, particularly the frontal lobes. There is a negative correlation between hemorrhage extent and GCS, but lesions are also detectable in patients with GCS of 15. On average, hemorrhages decrease by approximately 50% at one year and many patients retain >50% of the original lesion number/volume. [Support from NIH/NINDS:R01-NS054001].

Key words
hemorrhage, MRI, one-year follow-up, pediatric, susceptibility-weighted imaging, TBI

A2-05

ACUTE SUSCEPTIBILITY-WEIGHTED MRI OF HEMORRHAGIC BRAIN LESIONS AND ONE-YEAR NEUROPSYCHOLOGIC OUTCOMES AFTER PEDIATRIC TBI

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We present an update on acute hemorrhagic injuries detected by MRI susceptibility-weighted imaging (SWI), and their relation to one-year neurologic and neuropsychological outcomes in 52 prospectively studied pediatric TBI patients.

Pediatric patients, aged 4 to 18, were enrolled if they sustained a moderate/severe TBI (GCS score <13 or hemorrhagic intracranial injury on CT). Patients underwent MRI (at 3.0 Tesla), acutely (6–17 days). The number and volume of hemorrhagic lesions at initial MRI were compared to neurologic (PCPCS) and neuropsychological outcomes at 12 months, specifically general measures of memory utilizing the Children's Memory Scale (CMS: General Memory score), attention utilizing the Test of Everyday Attention for Children (TEA-CH: Teach G score), and the Wechsler Abbreviated Scale of Intelligence (WASI: Full Scale IQ).

We studied 52 children (38 males and 14 females, mean age 12.3 years), who were injured in vehicle/bike accidents (31), falls (12), sports-related injuries (7), or assaulted (1). The number/volume of lesions in all brain regions were negatively correlated with one-year PCPCS as well as one-year TEA-CH scores. Lesions in the corpus callosum were negatively correlated with FSIQ. Lesions in the frontal lobes and basal ganglia were negatively correlated with one-year CMS General Memory scores.

The extent of hemorrhagic brain lesions on acute MRI correlated with one year neurologic outcomes. Neuropsychologic assessment showed significant negative correlations between lesions in all brain regions and attention scores. Callosal lesions correlated with diminished Full Scale IQ scores, and lesions in the frontal lobes and basal ganglia correlated with diminished memory scores. SWI confirms that hemorrhagic shearing injuries have an important effect on many cognitive and neurologic domains. SWI can also be used in future models to predict long-term neuropsychological outcomes. [Support from NIH/NINDS:R01-NS054001].

Key words
hemorrhage, MRI, outcomes, pediatric, susceptibility-weighted imaging, TBI

A2-06

MULITIMODAL NEUROIMAGING WITH HYPERCAPNIA TO MONITOR CEREBROVASCULAR FUNCTION AFTER TRAUMATIC BRAIN INJURY AND EVALUATE TREATMENT

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Damage to the cerebral microvasculature is a major contributor to the pathophysiology of traumatic brain injury (TBI). In order to facilitate translation of pro-angiogenic therapies into clinical trials, there is a need to develop non-invasive biomarkers capable of monitoring cerebrovascular function over time and evaluating response to therapeutic intervention. Our objective was to develop a pre-clinical model that allows rapid assessment of candidate drugs and that can be adapted to the bedside. Regional differences in cerebrovascular reactivity to carbon dioxide (CVR_{CO2}) were examined using multimodal magnetic resonance imaging (MRI), including Blood Oxygen Level Dependent (BOLD) Imaging, Arterial Spin Labeling (ASL), and Susceptibility Weighted Imaging (SWI), in young adult male rats subjected to moderate fluid percussion injury and treated with sildenafil (Viagra) or saline. The temporal profiles of lesion volume and regional CVR_{CO2} were compared to histological measures and neurobehavioral outcome. The effects of dexmedetomidine and isoflurane anesthesia on CVR_{CO2} were also compared in healthy animals. Recommendations to optimize the design of hypercapnia neuroimaging studies and avoid potential pitfalls are provided.

Key words
angiogenesis, cerebrovascular reactivity, hypercapnia, MRI, sildenafil, treatment

A2-07

MULTISENSORY COGNITIVE CONTROL IN AN FMRI STUDY OF MTBI

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Mild traumatic brain injury (mTBI) has been associated with both deficits in cognitive control and neurosensory dysfunction. Multisensory cognitive control tasks presented at low (0.33 Hz) and higher (0.66 Hz) frequencies can evaluate whether dysfunction occurs in response to basic stimulus properties or as an interaction between unisensory cortex and cognitive control (attention-related modulations; ARMs). During a multisensory Stroop task, behavioral and functional magnetic resonance imaging data were collected on a group of 48 mTBI patients approximately 2 weeks post injury and 48 matched healthy controls (HC). An increased incidence of vestibular (43% vs. 10%) and visual (26% vs. 7%) symptoms were self-reported in patients relative to HC ($p < 0.05$), whereas no significant differences existed for auditory symptoms (5% vs. 2%). Basic sensory integrity (difference between high and low frequency trials) and ARMs were

evaluated in primary and secondary auditory (A1; A2) and visual (V1; V2) cortices using 2×2 (Group×Cue/distracter congruency) mixed measures ANCOVA analyses with simple effects performed to follow-up on significant interactions. No differences existed between groups on median reaction time and accuracy. Functional results indicated increased sensory response in V1 (trend) and V2 (significant) for mTBI patients in response to increasing stimulus frequency. In contrast, trend evidence of a reduced sensory response was present in A1 for patients. A similar pattern was observed for ARMs in visual (mTBI > HC) and auditory cortex (HC > mTBI) during congruent trials. These findings suggest a potential correlation between the greater incidence of visual symptoms during semi-acute mTBI in contrast to self-reported normal auditory functioning. The current research supports the use of ARMs derived from a multisensory cognitive control task as a putative central nervous system biomarker for identifying neurosensory deficits in mTBI, potentially even in the absence of measurable behavioral deficits.

Key words
fMRI, mTBI, multisensory, neurosensory deficits

A2-08

MANGANESE ENHANCED MRI FOLLOWING TRAUMATIC BRAIN INJURY

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Manganese is a calcium analog and MRI contrast agent. The purpose of this study was to evaluate the utility of manganese-enhanced MRI (MEMRI) in hyperacute, acute, and subacute phases of experimental moderate TBI. $MnCl_2$*$4H_2O$ was infused at a rate of 1.8 mL/hr for 30 minutes before TBI via tail vein at doses of 87.5 mg/kg (n = 4) or 29.17 mg/kg (n = 4). Anesthetized male rats underwent a 6mm craniotomy over the left primary forelimb somatosensory cortex and were impacted using a cortical impactor (impact velocity: 5 m/s; 250us dwell time; and 1mm depth) mimicking a moderate TBI. Additional $MnCl_2$ was given on days 1, 6 and 13 after TBI (24 hrs before subsequent MRI). MRI was performed 1–3 hrs and 1, 2, 7, and 14 days after TBI to acquire T_2 maps and manganese enhanced T_1-weighted images. We found the 87.5 mg/kg dose yielded some mortality and negatively affected behavioral performance. The 29.17 mg/kg dose was well tolerated, had no negative effects on behavioral performance, and yielded good MRI signal contrast. On day 0, T_2 MRI showed mild hyperintensity immediately underneath the impacted area. In contrast, MEMRI showed marked hyperintensity in and around the impacted area, extending beyond the impacted site. The sources of MEMRI contrast is likely due to disrupted BBB and/or spreading depolarization following TBI on day 0. T_2 MRI showed the largest change on day 2. On days 2, 7, and 14, MEMRI in the impacted area was heterogeneous with hypointense and hyperintense regions compared to normal tissue suggesting regions with enhanced and reduced calcium activities. Heterogeneous contrasts in the area surrounding the lesion on days 7 and 14 could be due to functional reorganization of neurons or glial scarring. MEMRI provides novel and useful MRI contrast to study TBI. MEMRI detects earlier and more sensitive changes than T_2 in the hyperacute phase. MEMRI could be sensitive to BBB permeability, spreading depolarization, functional reorganization, and glial scarring. Future studies will need to cross validate these findings with immunohistology.

Key words
contrast agent, manganese, MRI, TBI

A2-09

MRI REVEALS WIDESPREAD DISRUPTIONS IN CBF AND VASCULAR REACTIVITY FOLLOWING FOCAL TBI

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The goal of this study is to investigate cerebral blood flow (CBF), Diffusion, T_2, and vascular responses to 5% CO_2 inhalation in a mild TBI model in rats. Rats (n = 8) underwent a 6mm craniotomy over the left primary motor/somatosensory cortex and were impacted using a pneumatic cortical impactor (impact velocity 5.0 m/s, 250 μs dwell time, and 1mm depth) mimicking a moderate TBI. CBF, Fractional Anisotropy (FA), Apparent Diffusion Coefficient (ADC), T_2, and 5% CO_2 responses were longitudinally monitored on 0, 2, 7, and 14 days post-TBI. TBI induced widespread, severe heterogeneous perfusion disruptions beyond the impact ROI in the acute phase (first 3 hours). In the lesion, CBF dropped to 20% of normal 1–3 hrs post-TBI, increased to 140% of normal on day-2 (hyperperfusion), and returned toward normal on day-7 and 14. CBF actually decreased with CO_2 inhalation. CO_2 responses varied between both cortices at 1–3 hrs and day-2. ADC increased, T_2 increased, and FA decreased 1–3 hrs and day-2 post-TBI. In the perilesional regions, CBF dropped to 60% of normal 1–3 hrs post-TBI, remained depressed on day-2, and returned toward normal on day-7 and 14. CO_2 response was attenuated at 1–3 hrs and day-2, and recovered by day-7 and 14. ADC, FA, and T_2 values did not change. In summary, CBF and CO_2 response disturbances were extensive while T_2, FA and ADC changes were limited only to the area of impact. For FA, ADC, and T_2 to change, CBF must reduce to 20% of normal for a substantial duration. No changes in these MRI parameters were detected if CBF dropped to 60% of normal up to 14 days post-TBI. Multimodal MRI offers complementary, clinically relevant information to probe tissue condition following TBI and can provide useful information to further characterize TBI.

Key words
cerebral blood flow, MRI, TBI, vascular reactivity

A2-10

RESTING-STATE BRAIN ACTIVITY IN MILD TBI PATIENTS WITH HIGH VERSUS LOW POST-TRAUMATIC STRESS DISORDER SYMPTOM SEVERITY

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The objective is to use magnetoencephalography (MEG) to identify electrophysiological patterns that characterizes the presence and severity of symptoms from post-traumatic stress disorder (PTSD) in military service members with mild traumatic brain injur (mTBI) in resting state brain activity.

Service members (n = 23) injured in Iraq and Afghanistan, diagnosed with mTBI were evaluated for PTSD, PTSD Check List-Military (PCL-M) score ≥ 50, during intake at the National Intrepid Center of Excellence four-week interdisciplinary intensive outpatient program. Resting-state 5 min MEG recordings were acquired in two subject groups: Group 1 comprised participants with *high* PTSD symptom severity scores (n = 12, mean 61.8 ± 8.0); Group 2 comprised participants with *low* PTSD symptom severity scores (n = 11, mean 39.5 ± 6.5). Independent component analysis was used to remove

movement interference and data were band-pass filtered in delta (0.75–4 Hz), theta (4-7 Hz), alpha (8-13 Hz), beta (16-24 Hz) and gamma (25-40 Hz) frequency bands. Cortical surface was determined from MR T1 images using FreeSurfer. The cortical distribution of the mean signal power in each frequency band was estimated and integrated over 68 cortical regions (Desikan-Killiany atlas), and the regional power was contrasted between groups.

Increased delta oscillatory activity was observed in Group 1 in bilateral regions of the medial temporal lobe (entorhinal and parahippocampal cortex, and isthmus of the cingulate gyrus). Increased gamma activity was also observed in visual cortical areas. A *decrease* in theta and alpha activity was observed in Group 1 in regions of the left inferior frontal gyrus, and left lateral temporal cortex.

Our observations support a neurobiological model that posits hyperactivity in regions of the limbic system in patients with PTSD, accompanied by low oscillatory activity in frontal and temporal brain regions that can have a role in the regulation of the limbic system reactivity.

Key words
magnetoencephalography, MRI, mTBI, PTSD

A2-11

NETWORK-BASED ANALYSIS OF STRUCTURAL CONNECTIVITY REVEALS ALTERED BRAIN ORGANIZATION AFTER EXPERIMENTAL BRAIN INJURY

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Altered axonal integrity is a well-known marker of traumatic brain injury that can be visualized by diffusion tensor imaging (DTI). Our prior studies in the rat controlled cortical impact (CCI) model indicate that tract-based statistical analysis (TBSS) of DTI data underestimates the extent of axonal injury when compared to silver-staining histochemical studies of other labs. We tested whether a quantitative analysis of DTI-based brain networks would provide a more sensitive indicator of axonal damage and if alterations in network connectivity might also underlie TBI dysfunction. We employed TBSS and graph theory measures of brain connectivity to assess DTI data acquired before and at 28 days after moderate CCI-injury in rats ($n=17$). TBSS revealed alterations in fractional anisotropy, radial, axial and mean diffusivity that was restricted to the ipsilateral corpus callosum ($P<0.05$). Network analysis revealed a trend towards globally increased characteristic path length (CPL, $P=0.056$), significant global increases in normalized CPL (1.27 ± 0.02 vs 1.35 ± 0.03), decreases in network efficiency ($1.32e^{-2}\pm2.3e^{-4}$ vs $1.26e^{-2}\pm1.89e^{-4}$) but no difference in the clustering coefficient (all two-tailed t-tests, $P<0.05$). One potential explanation for this is reduced long-range connections. As expected, measures of local connectivity were largely in agreement with the TBSS data ipsilaterally, with reductions in network strength, betweenness_centrality, clustering_coefficient and regional and local efficiency ($P<0.05$, one-tailed FDR-corrected). However, unlike the TBSS data, there were also notable reductions in many of these measures within contralateral regions (M2, S1, Cg1/2), bilaterally in the PF-cortex, as well as the fimbria, posterior RSG-cortex and the hypothalamus suggesting much wider decreases in anatomical connectivity. More unexpectedly, when we re-ran the analysis using the more stringent two-tailed-t-test, in addition to most of the prior network deficits, we found significant increases in ''hubness'' and strength of connectivity bilaterally in M1 cortex and thalamus, implying potential spontaneous reorganization at the structural level. Partial agreement from our functional connectivity data (see accompanying abstract) would appear to support this conclusion. Support: UCLA_BIRC.

Key words
connectivity, DTI

A2-12

TEMPORAL ALTERATIONS IN FUNCTIONAL CONNECTIVITY AFTER EXPERIMENTAL TRAUMATIC BRAIN INJURY

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Spontaneous resolution of sensory-motor behavioral deficits following TBI is a well-known phenomenon that occurs both after experimental and clinical TBI. Our prior functional MRI (fMRI) data has shown that reorganization of brain circuits is an important component of this. However, use of evoked fMRI to study cortical map plasticity only allows one circuit to be studied so that a limited snapshot of circuit reorganization is permitted. On the other hand, resting state fMRI (rsFMRI) allows an unbiased view of brain functional connectivity (fc) across multiple brain networks so that it might provide a useful approach to understanding brain functional reorganization after injury. We therefore acquired rsFMRI data before, and at weekly intervals until 4-weeks after unilateral CCI injury over the forelimb sensorimotor cortex in adult, male rats ($n=9$). Using group-wise independent component analysis (ICA) to identify the major networks and with verification using seed-based correlation analysis, we found that unlike many of the bilaterally present cortical and subcortical networks observable before injury, the number of cortical networks were reduced ipsi-lesionally at 7-days after injury and those present were enlarged (voxel-based analysis, $P<0.05$), suggesting reduced intrahemispheric and increased intra-cortical fc, in agreement with our prior structural fc data in this model. Despite the confinement of primary injury to cortical areas, caudate fc was significantly reduced ipsi-lesionally at 7-days and this persisted through 4-weeks post-injury indicating more widespread dysfunction than previously seen ($P<0.05$). Between 7 and 28 days there was an ipsi-to-contra-lesional shift in the cortical components so that only 1 minor, ipsi-lesional anterior motor network remained, while the contra-lesional cortex components were more numerous and similar to pre-injury. We also used graph theory methods to quantify network-level disturbances in more detail using anatomically-defined nodes from a co-registered, segmented brain atlas. Results were largely in agreement with the ICA analysis with regard to decreased connectivity, but in addition, increased local connectedness across novel nodes was apparent at 28 days within the ipsi-lesional hemisphere. Support: UCLA BIRC

Key words
connectivity, connectomics, resting state fMRI

A2-13

RECRUITMENT, SCREENING, AND CLASSIFICATION OF ACUTE TBI: ADVANTAGES OF A MULTI-PATHWAY SCREENING PROTOCOL

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Inconsistency in diagnosis and medical documentation of TBI presents a significant obstacle to recruitment of patients for acute and subacute therapeutic trials. Three unproven constructs were implemented: variable recruitment ''pathways'' appropriate to each population identified, a ''TBI Evidence'' assessment standardized across populations, and research MRI in the acute period.

Acute TBI patients were recruited at four clinical sites (Bethesda Suburban Hospital, Washington Hospital Center, Virginia Commonwealth University Hospital, and University of Maryland Shock Trauma Center). Sub-acute and chronic patients were recruited through NIH Clinical Center or by telephone. A locally developed TBI evidence assessment was used to classify subjects into groups (Definite/Probable/Possible) by best available evidence supporting a TBI diagnosis. Severity was classified according to DOD/VA clinical practice guidelines, with the addition of ''Complicated Mild'' based on imaging abnormalities.

During the one-year study period, 278 subjects were enrolled; 186 (67%) at acute sites, 46 (17%) at NIHCC, and 46 (17%) by telephone. Median age was 47 (IQR 31-57) years, 40% were female, and 31% belonged to racial minorities. Median time-from-injury to MRI was 59 (IQR 24-216) hours overall and varied between acute sites (26–69 hours), in contrast to NIHCC (8 years). Approximately one-half of subjects with imaging at NIHCC and acute sites had TBI-related abnormalities on CT or MRI. TBI severity across all pathways was 35% mild, 26% complicated mild, 22% moderate, 10% severe, and 7% unclassified. 68% of subjects had Definite TBI.

The multi-pathway approach, coupled with acute MRI, provides a diverse pool of well-characterized TBI subjects for referral to interventional and observational studies.

Key words
classification, early MRI, multi-site, recruitment, screening

A2-14

CHARACTERIZING TBI RADIOLOGY READS USING THE ANNOTATION AND IMAGE MARKUP PLATFORM

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Standardizing clinical reads of diagnostic images acquired from TBI patients is an important step towards enabling systematic characterization of radiological findings across multiple sites and research studies. Annotation and Image Markup (AIM) software is a freely available software package for performing computerized entry of structured radiological interpretations while simultaneously allowing visualization and annotation of the imaging data. In this work, we report on the results of employing this software for the CNRM Screening Protocol, a study involving MR and CT imaging collected from 5 different sites. Inclusion criteria for this protocol allow for any participant 18 years or older having symptoms of concussion, TBI, post concussion syndrome, or post concussion disorder. Findings of each patient were compared to the clinical reads.

Images were read by a neuroradiologist using a release of the AIM workstation developed especially for TBI. A template was created for entering the radiological interpretations based on an abbreviated version of the NINDS CDE's. The following radiological findings were considered: 1) TBI, 2) microbleeds, 3) extraparenchymal hemorrhage, 4) contusion, 5) diffuse axonal injury, and 6) encephalomalacia.

A total of 276 scans (186 CT, 90 MRI) were evaluated and compared to their clinical reads. The clinical comparison was obtained by manually extracting relevant information from the clinical radiology read available in the patient's medical record. Overall, 208 reads (75.4%) yielded identical results compared to the clinical reads, while 68 (24.6%) were different in one or more categories. Findings were similar except for microbleeds, which was much higher in the AIM reads (30% vs. 6%)

The AIM platform provides a convenient informatics solution for structured radiology reads in TBI studies.

Key words
CT, imaging, MRI, TBI

A2-15

CONNECTOME-SCALE ASSESSMENTS OF STRUCTURAL AND FUNCTIONAL CONNECTIVITY IN MILD TRAUMATIC BRAIN INJURY AT THE ACUTE STAGE

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Mild traumatic brain injury (mTBI) is difficult to diagnose in emergency setting due to the negative findings in clinical imaging in most mTBI patients. Several functional network alternations have been reported in mTBI; however, the large scale network alternations, particularly at connectome scale, is still unknown. In this study, we adopted a novel approach to analyze both structural and functional network changes at connectome level in mTBI patients.

Forty (40) mTBI patients and 50 demographically matched healthy subjects were recruited in our local hospital. The patients were scanned at the acute setting before their discharge. Both diffusion tensor imaging (DTI) and resting state functional magnetic resonance imaging (fMRI) data were acquired. In data analysis, a novel approach called DICCCOL (dense individualized and common connectivity-based cortical landmarks) was applied. Each DICCCOL node is a functional landmarker with consistent white matter (WM) fiber connection profile across individuals and thus preserves the same functional role across individuals.

Among 358 nodes on DICCCOL templates, 41 nodes were identified as discrepant DICCCOL nodes. The WM pathways associated with these discrepant nodes include corpus callosum, superior and inferior longitudinal fasciculi, cincuglum, arcuate fasciculus, and dorso lateral frontal white matter. Functional connectivity analysis of the common 317 nodes showed 60 functional connectivities as the most distinctive and discriminative features of our data to differentiate patients from healthy controls, labeled as connectomic signatures.

These connectomic signatures gave 93.75% sensitivity and 100% specificity. Analysis of functional domains showed decreased intra-network connectivity within emotion network and ''emotion-cognition'' interaction. It also showed increased interactions among ''action-emotion'' and ''action-cognition'' as well as within perception networks.

This is the first effort of connectomic scale analysis of both structural and functional networks in mTBI. Multiple fiber tracts and functional networks are affected in mTBI patients in the acute setting.

Key words
connectome, functional connectivity, neuroimaging, traumatic brain injury

A2-16

DIFFUSE WHITE MATTER TRACT ANOMALIES IN AGING BUT CLINICALLY NORMAL RETIRED ATHLETES WITH A HISTORY OF SPORTS-RELATED CONCUSSIONS

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Sports-related concussions are thought to lead to persisting subclinical anomalies of the motor and cognitive systems in young asymptomatic athletes. In advancing age, these latent injuries correlate with detectable motor and cognitive function decline. Until now, the interacting effects of concussions and the normal aging process on white matter integrity remain unknown. Here we used a tract-based spatial statistical method to uncover potential white matter tissue damage in retired athletes with a history of concussions, free of comorbid medical conditions. We also investigated potential associations between white matter integrity and declines in cognitive and motor functions. Compared to an age-and-education-matched control group of retired athletes without concussions, former athletes with concussions exhibited widespread white matter anomalies along many major association, interhemispheric and projection tracts. Group contrasts revealed decreases in fractional anisotropy and increases in mean and radial diffusivity measures in the concussed group. These differences were primarily apparent in fronto-parietal networks as well as in the frontal aspect of the corpus callosum. The white matter anomalies uncovered in concussed athletes were significantly associated with a decline in episodic memory and lateral ventricle expansion. Finally, the normal association between frontal white matter integrity and motor learning was absent in concussed participants. Together, these results show that the aging process in retired athletes with a history of sports-related concussions is linked to diffuse white matter abnormalities that are consistent with the effects of traumatic axonal injury and exacerbated demyelination. These changes in white matter integrity might explain the cognitive and motor function declines documented in this population.

Key words
cognition, diffusion tensor imaging, normal aging, sports-related concussions

A2-17

EARLY MRI FINDINGS AND 1-YEAR OUTCOMES IN PEDIATRIC COMPLICATED MILD TBI

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We present MR imaging findings on a subgroup of pediatric TBI patients who had CT evidence of intracranial hemorrhage despite ''mild'' GCS scores, and their relation to one-year neurologic and neuropsychological outcomes.

Pediatric patients, ages 4 to18 years, were enrolled if they sustained a moderate/severe TBI (defined by GCS score < 13 **or** hemorrhagic intracranial injury on CT). Patients underwent 3.0T MRI, acutely (6–17 days), including susceptibility-weighted imaging (SWI), MRS and DTI. The number and volume of hemorrhagic lesions, regional DTI metrics (FA, ADC, AD, RD) and MRS ratios (NAA/Cr, NAA/Cho, Cho/Cr) were compared to neurologic (PCPCS) and neuropsychological outcomes at 12 months, specifically general measures of memory utilizing the Children's Memory Scale (CMS: General Memory score), attention utilizing the Test of Everyday Attention for Children (TEA-CH: Teach G score), and the Wechsler Abbreviated Scale of Intelligence (WASI: Full Scale IQ). Patients with intracranial hemorrhage and GCS of 13–15 were examined separately.

Twenty-two children had ''mild'' GCS scores of 15 (n = 17), 14 (n = 3) or 13 (n = 2). They were injured in vehicle/bike accidents (9), falls (8), sports-related injuries (4), or assaulted (1). In this subgroup, the average number (32) and volume (2.5 cc) of hemorrhagic lesions were lower than the larger group of 52 patients (87 lesions, 12.0 cc hemorrhage) and did not show correlation with neuropsychologic measures at 1-year. ADC values in the deep hemispheric regions (basal ganglia, thalami, corpus callosum) and global NAA/Cr ratios were significantly different in these children, compared to control subjects. All 22 patients had good neurologic outcomes. FA values in subcortical white matter were significantly correlated with attention scores at one-year.

There are limitations to the GCS score, particularly with regards to TBI patients with milder injuries. These children can have imaging abnormalities that correlate with neuropsychological measures at one-year follow-up. Support from NIH/NINDS:R01-NS054001.

Key words
diffusion tensor imaging, magnetic resonance spectroscopy, mild traumatic brain injury, pediatric, susceptibility weighted imaging

A2-18

CEST-MRI IS SENSITIVE IN NON-INVASIVE DETECTION OF GLUCOSE, LACTATE, AND GLUTAMATE + GLUTAMINE INTERRELATION IN MILD CLOSE HEAD TBI

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The energy supply and consumption is crucial for survival of traumatized brain tissue. Chemical exchange saturation transfer (CEST) MRI experiment was deployed to study mild TBI responses of three metabolites, glucose, lactate, and glutamate + glutamine (Glx), by quantifying the asymmetry of the CEST effects. 12 TBI animals were imaged at baseline, 1DPI, 3DPI and 8DPI for metabolites in

cortex(CT) and corpus callosum(CC). After MRI, animals were perfused for IHC examinations of neurofilaments(SMI31), myelination(MBP), microgliosis(IBA1) and astrogliosis(GFAP).

Compared to baseline, glucose drastically decreased 50% at 1DPI in CT($p < 0.01$) and gradually decreased 30% at 8DPI in CC($p < 0.01$). Lactate in CT significantly decreased to the lowest level($\sim 55\%$) at 1DPI($p < 0.01$), and gradually increased to the baseline level at 8DPI. The Glx group in CT decreased 30% after injury at 1DPI($p < 0.05$) and remained low at both 3DPI and 8DPI($p < 0.05$). Similarly in CC, lactate and the Glx groups decreased at 1DPI($\sim 30\%$, $p < 0.05$), reached the lowest at 3DPI(30%, $p < 0.01$), then slightly increased at 8DPI($p < 0.05$). Although the trends of the IHC analysis were not significant, a gradual decrease of SMI31 and MBP, and increase of microgliosis and astrogliosis were observed.

Comparable to previous reports, glucose largely decreased after trauma, and glutamate may regulate glycolysis in astrocytes and influence lactate release in supporting the increased energy demand in the traumatized tissue. Different patterns of glutamine, lactate and glucose interrelations were found between gray and white matter, indicating that the interrelation patterns may be specific to the tissue and type of TBI. The early decrease of CEST effects on all metabolites suggests that the water content significantly increased from edema after inslut. IHC results indicate that the injury was mild to moderate in a pattern of slightly injured axon and myelin, and a slight increase of immuno response. These results indicate that the CEST-MRI asymmetry analysis is sensitive in reflecting the consequence of mild TBI, even when the convention IHC stainings do not show significant difference.

Key words
CEST MRI, glucose, glutamate, lactate, non-invasive

A2-19

TSPO-PET IMAGING AFTER TRAUMATIC BRAIN INJURY IN MICE

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Positron emission tomography (PET) imaging of the translocator protein 18 kDa (TSPO) is recognized as a clinical means to detect and investigate neuroinflammation. It is widely considered that TSPO PET signal reveals not only reactive microglia but also astrocyte. However, it is still unclear how to interpret uptake of TSPO PET signals after traumatic brain injury (TBI) which involved peripheral immune cell recruitment.

We aimed to determine what types of cells expressed TSPO uptake after TBI.

Controlled cortical impact (CCI) was induced in the cerebral hemisphere of adult male C57B6/J mice. Sham and CCI operated mice were investigated by [^{18}F] PET from 1 day to 9 weeks after injury. Regions of interest were placed on the injured site of the PET/CT fused images. Max standardized uptake values (SUV max) in this area were calculated. Furthermore, the ratio of cells infiltrated into the injured cortex was analyzed by flow cytometry, and localization of those cells was also analyzed by Immunohistochemistry.

TSPO uptake started to increase around the injured site after injury, focused toward the injured core at 1 week after injury and redistributed around the cavitation of contusion afterword. SUV max indicated a bimodal increase at 7 days post injury and 6 weeks post injury. Flowcytometric study showed that Gr-1^{+} /Ly-6C^{high} macrophages increased from 1 day to 3 days post injury and decreased rapidly. Immunohistochemistry analysis showed TSPO uptake co-localized by reactive microglia.

Our results suggested the first peak of TSPO uptake at 1weeks after injury showed the phagocytosis of cell debris and the second peak at 6 weeks post injury indicated the glial scar formation. TSPO-PET has the possibility to be an imaging technique to monitor neuroinflammation after TBI.

Key words
astrocyte, microglia, PET, TSPO

A2-20

POST-TBI ALTERATIONS IN FRONTO-LIMBIC MORPHOMETRY ARE ASSOCIATED WITH DEPRESSION

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Post-traumatic depression (PTD) is a common neurobehavioral complication following traumatic brain injury (TBI). Studies shows volumetric alterations in fronto-limbic brain regions are associated with depressive symptomology. This study examined fronto-limbic brain morphometry in TBI as a possible biomarker of PTD susceptibility, hypothesizing a reduction in these regions post-TBI. Structural MRI scans were acquired 1–3 years post-TBI in 40 adults with moderate/severe TBI and 33 age-matched controls. Regional brain volumes were calculated using automatic segmentation software (FreeSurfer). A subset of individuals with TBI (cases, $n = 21$) were assessed for depressive symptomology using the Patient Health Questionnaire (PHQ-9). Mann-Whitney and Spearman correlations were used as appropriate. Data were corrected for multiple comparisons. Within cases, volumes in the amygdala (right, $p = 0.005$; left, $p = 0.058$) and hippocampus (bilaterally, $p < 0.001$) were reduced compared to controls. Correlations between regional volumes also differed among cases compared to controls. Among cases, left amygdala volume was positively correlated with left hippocampus ($r = 0.42702$, $p = 0.015$) and left caudal anterior cingulate volume ($r = 0.36604$, $p = 0.0421$), while these correlations were non-significant among controls. However, bilateral amygdala volumes were less correlated with medial orbitomedial cortex volumes in cases compared to controls. Interestingly, subjects with PTD showed larger left amygdala volumes ($p = 0.005$) compared to those with no depression. We suggest relative regional atrophy within fronto-limbic circuits following TBI may result in altered volume correlations. This relative TBI-related fronto-limbic regional atrophy may represent a possible PTD susceptibility following TBI. Future studies need to validate these findings in larger populations, examining how fronto-limbic regional volumes may reflect fronto-limbic circuit function and relate to PTD susceptibility.

Funding: NIDRR-H133A120087, DOD-W81XWH-071-0701, NIH-R01HD048162, NIH-R01NS048178, NIH-R01NS049142.

Key words
depression, limbic systems, neuroimaging, traumatic brain injury

A2-21

CEREBROVASCULAR DYSFUNCTION AFTER TRAUMATIC BRAIN INJURY: ASSESSMENT WITH MRI AND NIRS

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Injury to small and medium-sized cerebral blood vessels is a recognized consequence of traumatic brain injury (TBI). Clinical trials of therapies directed at diffuse vascular injury (DVI) will require quantitative, non-invasive methods to measure cerebrovascular reactivity (CVR), to select patients likely to benefit and to demonstrate physiologic efficacy in early phase clinical trials. Measurement of the Blood Oxygen Level Dependent (BOLD) response to hypercapnia, using magnetic resonance imaging (MRI) or Near Infrared Spectroscopy (NIRS) shows promise as a biomarker for DVI-directed theapies.

23 patients with moderate to severe TBI were studied during the chronic stage (>6 months) after injury. 12 age and gender matched uninjured controls were also studied. Region-specific CVR was assessed using a hypercapnia challenge. Inhaled gas alternated between room air and 5% carbon dioxide (CO_2) mixed with 21% O_2/74% N_2 every minute in a block design. Hemodynamic response function was acquired for 7 minutes using both MRI (whole brain) and NIRS (frontal regions) in two separate sessions. End-tidal ($EtCO_2$) was monitored continuously during the experiment using a capnograph and used as a regressor in the analysis. Mean (SD) CVR measured with BOLD-MRI was 0.31 (0.05) %BOLD/mmHg for the controls, and 0.25 (0.12) %BOLD/mmHg for TBI subjects ($p=0.03$). With NIRS, CVR was 2.7 (0.3) μM/mmHg for controls and 1.7 (0.6) μM/mmHg for TBI subjects ($p=0.01$). Within subjects, CVR measured using BOLD-MRI correlated highly with CVR measured with NIRS ($r=0.83$, $p<0.0001$).

We conclude that measurement of CVR with either MRI or fNIRS is practical and reliable. Patients in the chronic stage after TBI have blunted and highly variable CVR. CVR measurements with either method show promise as a biomarker for DVI-directed therapies.

Key words
BOLD-MRI, cerebrovascular reactivity, near-infrared

A2-22

CORRELATIVE MR AND PET-FDG IMAGING OF LESION AND CONTRALATERAL CORTEX IN CONTROLLED CORTICAL IMPACT BRAIN INJURY

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Traumatic brain injury (TBI) diagnosis is primarily dependent on computed tomography (CT) to indicate injury severity. However, other modalities such as magnetic resonance imaging (MRI) and positron emission tomography (PET) may provide improved sensitivity and specificity for TBI. In the present study, imaging parameters from MRI and PET were utilized to assess lesion and cortical properties after a controlled cortical impact (CCI) brain injury in a rat. Male Sprague Dawley rats ($N=24$) received a moderate CCI and underwent T2-weighted, diffusion-weighted (DW), arterial spin labeling (ASL) MRI and ^{18}F-fluorodeoxyglucose (FDG)-PET imaging at baseline and at multiple time-points post-injury. Lesion volumes were measured using a semi-automated algorithm and compared to manually determined volumes on the images and on histology. T2-values, apparent diffusion coefficient (ADC), cerebral blood flow (CBF) and FDG uptake were obtained for lesion and contralateral cortex. Lesion volume measurements were significantly correlated for the algorithm, manual, and histological methods ($ICC=0.92$). This result demonstrates that T2 maps with semi-automated methods can be used for an objective determination of TBI lesion volume. Uncoupling between CBF (decrease) and FDG uptake (increase) was detected in the lesion at days 7–8 along with vasogenic edema marked by elevated T2 and ADC values. Uncoupling was also detected in the contralateral cortex at day 11 but with cytotoxic edema indicated by elevated T2 values and decreased ADC. In addition, cytotoxic edema was also measured at day 2 in the contralateral cortex, possibly serving as a marker for injury severity. Taken together, lesion volume, edema (T2, ADC), and uncoupling (CBF, FDG) measurements may provide researchers with a multiparametric model to stage or grade injury severity and to possibly serve as a prognostic indicator of outcomes.

Key words
arterial spin labeling, contralateral cortex, controlled cortical injury, diffusion-weighted imaging, lesion volume, PET imaging, T2-weighted imaging

A2-23

BASELINE ALTERATIONS OF MEDIAL TEMPORAL LOBE SUBSTRUCTURES IN CONTACT-SPORT ATHLETES

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There is a high incidence rate of mild traumatic brain injury in contact-sport athletes, such as football players. Understanding the relationship between traumatic forces and brain injury may enable the prevention of permanent cognitive deficits, and possibly even disorders such as chronic traumatic encephalopathy (CTE). Neuropathologically, CTE is characterized as a tauopathy with atrophy of the many portions of the brains, including the medial temporal lobes (MTL). Our objective was to determine if there were differences at baseline in MTL structures in football players that likely have a long history of concussive and sub-concussive forces compared to athletes who play a non-contact sport such as volleyball. At the beginning of their season and across two seasons, 47 football and 21 volleyball players were scanned on a GE 3.0T whole-body scanner. Imaging sequences included a 1.0x1.0x1.0 mm T1 volume as well as a 0.4x0.4x2 mm oblique coronal T2-weighted FSE volume. We used the software Automatic Segmentation of Hippocampal Subfields (ASHS) to segment the hippocampus and parahippocampal sub-regions. We blindly edited the segmentations to (1) ensure exclusion of the amygdala, (2) extend out hippocampal body/head subfields to encompass the entire

structure when occasionally undersegmented, and (3) ensure proper delineation of the hippocampal head/body, wherein the head was considered to be any coronal slice in which the uncus was even partially visible. The CA2 and CA3 subfields and the parahippocampal gyrus (PHG) and entorhinal cortex were subsequently combined into CA23 and PHG respectively. These volumes at baseline were assessed in a multiple regression, using supratentorial volume and age as covariates of non-interest. The volume of both hippocampal heads was found to be lower in football players compared to volleyball players ($P = 0.0021$ left, 0.0254 right, uncorrected). Preliminary results suggest that MTL structures may be affected in contact-sport athletes, though it is unknown if this anatomic difference is secondary to the presumed long history of prior contact-sport exposure, or other factors. Future studies will include assessing hippocampal subfield volume changes in these athletes longitudinally.

Key words
hippocampus, traumatic brain injury

A2-24

QUANTIFYING WHITE MATTER INJURY IN TRAUMATIC BRAIN INJURY WITH HIGH DEFINITION FIBER TRACKING

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There is an urgent, unmet demand to pinpoint the location and quantify extent of damage in traumatic brain injury (TBI) with advanced neuroimaging. We have developed High Definition Fiber Tracking (HDFT), a 3T MRI-based diffusion spectrum imaging (DSI) and tractography analysis pipeline, to quantify axonal injury in TBI patients. The goal is to visualize white matter injury and correlate with neurologic outcomes.

Subjects in the chronic phase of TBI were recruited along with healthy volunteer control subjects. A novel homologue correlation methodology quantified tractography to estimate white matter integrity in patients and healthy controls. After reconstruction, bilateral hemisphere homologues of eight major tracts were segmented. Integrity of segmented tracts was estimated by calculating homologue correlation and tract spread, with subsequent quantification of left-right symmetry.

Forty-one subjects (23 TBI, 18 controls) were scanned with the HDFT DSI protocol. Both groups showed high correlations for all tracts. TBI patients showed reduced homologue correlation and tract spread and increased outlier count (correlations > 2.32 *SD* below control mean). On average, 6.5% of tracts in the TBI group were outliers, with substantial variability among patients. Number and summed deviation of outlying tracts correlated with initial Glasgow Coma Scale (GCS) score and 6-month Glasgow Outcome Scale – Extended (GOS-E) score, suggesting that correlation metrics can detect heterogeneous damage affecting a low proportion of tracts, presenting a potential mechanism for advancing TBI diagnosis.

Using HDFT imaging with quantitative analysis, we demonstrated high correlation of volume of white matter pathways in normal subjects, and select sites of loss of symmetry in TBI subjects. These results show TBI can be detected through quantifying loss of axonal symmetry, that the damage is heterogeneous, and that an outlier approach can capture such heterogeneous damage.

Key words
high definition fiber tracking, traumatic brain injury

A2-25

DIFFUSED TENSOR IMAGING METRICS IN ACUTE MILD TRAUMATIC BRAIN INJURY AND ITS CORRELATION WITH EARLY NEUROPSYCHOLOGICAL IMPAIRMENT

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Mild traumatic brain injury (mTBI) remains a contentious diagnosis as the outcome is not always homogenous, even in the absence of any visible intracranial lesions or injury through conventional magnetic resonance imaging (MRI). Various neuropsychological impairments are commonly reported in a subset of these patients.The availability of new techniques such as diffuse tensor imaging (DTI) enables better characterization of the extent of immediate microstructural changes post-mTBI.

We aimed to establish the correlation between the changes in fractional anisotropy (FA), mean diffusivity (MD) and early neuropsychological impairment in the immediate aftermath of mTBI.

Forty-seven patients with mTBI were prospectively recruited, along with 15 healthy controls. Anatomical MRI and structural DTI were performed on all patients with mTBI using a 3T MRI (within 24 hours from the time of trauma). The DTI volumes were registered to the ICBM DTI-81 white matter atlas. FA and MD values were automatically calculated for 16 white matter tracts. Comprehensive neuropsychological evaluation was done using the Neuropsychological Assessment Battery within the same admission.

Neuropsychological deficits including attention, language, executive function and memory were commonly seen in the patients' group. The changes in FA values of the anterior corpus collosum and left anterior internal capsule negatively correlated with memory-related impairments. The FA changes in uncinate fasciculus negatively correlated with the deficits of executive function. The decrease in FA and increase of MD in the medial lemniscus, corona radiata and superior longitudinal fasciculus negatively correlated with the attention and language deficits.

White matter abnormalities in the immediate aftermath of mTBI and its influence on higher cognitive functions needs to be further investigated for long term effects.

Key words
cognition, DTI, MTBI, neuropsychology

A2-26

MRI TARGETED PATHOLOGY OF ACUTE TBI

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Acute and longitudinal imaging after TBI reveals evolving injury to the brain. Interpretation of imaging findings is limited by availability of corresponding pathological study. A brain donated through the CNRM THINC study provided the opportunity to connect acute and follow-up MRI to pathology.

A 48-year-old man was found unresponsive after a bicycle accident. A right subdural hemorrhage (SDH) prompted urgent hemicraniectomy. The subject was consented and research MRI was obtained on days 2, 7, and 101. The patient expired seven months post-injury. Whole brain images were acquired (7T MRI) after formalin fixation. The brain was sliced and selected for embedding in paraffin based on MRI findings and large format tissue sections were mounted on oversized glass slides. Sections were stained using H&E, LFB H&E, and Perls iron. Using the 20x objective, histopathology sections were digitized with 32,000 image tiles in the entire tissue section using a microscope scanner. The resulting image files were compressed as hierarchical JPEG files and viewed using proprietary software to confirm abnormalities detected on MRI with lesions identified on the histological section from the tissue specimen.

In addition to SDH and subarachnoid hemorrhages, MRI showed temporal lobe contusions, linear-appearing hemorrhagic lesions in bilateral frontal lobes, microbleeds, and meningeal injury. Based on this evidence, the superior frontal gyrus was chosen as the region of interest. The results demonstrate use of acute MRI findings to target regions of interest for pathology. In-vivo imaging revealed a complexity of injury: pre-existing, primary injury due to acute event, and secondary progressive injury. From pathology alone, it would be difficult to reconstruct the timing of injury. Our approach integrates clinical data along with clinical and postmortem MRI that improves interpretation of the pathological progression.

Key words
acute injury, histopathology, imaging, MRI, pathology

A2-27

CROSS-SECTIONAL VOLUMETRIC COMPARISON OF MILD AND MODERATE TRAUMATIC BRAIN INJURY

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Neuroanatomical differences across classifications of TBI severity remain poorly understood. In this work, we examine the structural brain differences between moderate and mild TBI using both voxel-based morphometry (VBM) and regional volumes. Participants with TBI ranging from the sub-acute to the chronic stage underwent MRI during which high resolution (1 mm isotropic) T1-weighted images were acquired. Mean ages of the mild group ($N=16$, M = 6) and the moderate group ($N=21$, M = 16) were 43 ($SD=15.75$) and 47 ($SD=17.66$) respectively. Average time since injury in months was 8.56 for the mild group ($SD=7.81$) and 10.43 months ($SD=5.22$) for the moderate group. TBI classification was determined by a physician based on the DoD/VA Common Definition of Traumatic Brain Injury. Image analysis was performed using 1) SPM8 with the VBM8 toolbox and 2) FreeSurfer 5.3 for regional volumes. The VBM analysis consisted of comparisons of gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using 2-sample *t*-tests with age, time since injury and gender as nuisance variables. No significant differences were found between the groups in WM. However, the VBM analysis of GM showed reduced volumes in the moderate patients at the cluster-level ($p < 0.001$ unc.) for the right postcentral gyrus (pFWE = 0.002) and hippocampus (pFWE = 0.002), and for the amygdala (pFWE = 0.046). Lateral ventricles ($p < 0.001$ unc.) were also larger in the moderate group, with cluster-level significance at pFWE = 0.000. The FreeSurfer results corroborated that the moderate group had significantly smaller amygdala ($p < 0.01$) and hippocampi ($p < 0.001$), with larger lateral ventricles ($p < 0.001$). These differences in structure, particularly in the amygdala and hippocampus, suggest potential damage to pathways involved in memory and emotion, two areas that are commonly implicated in TBI. Future work will investigate these volumetric measures in relation to neurobehavioral measures.

Key words
cross-sectional, segmentation, TBI, TBI classification, voxel based morphometry

A2-28

LATERAL VENTRICLE VOLUME ASYMMETRY PREDICTS MIDLINE SHIFT IN SEVERE TRAUMATIC BRAIN INJURY

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Midline shift following traumatic brain injury (TBI) detected on acute CT scans is an established predictor of poor outcome. We hypothesized that lateral ventricular volume (LVV) asymmetry is an earlier sign of developing asymmetric intracranial pathology than midline shift. Since lateral ventricle size has individual variability, LVV ratio (LVR) was used.

A retrospective analysis on 84 adults with blunt, severe (GCS < 8) traumatic brain injury (sTBI), requiring a ventriculostomy was performed. Seventy-six of these patients underwent serial CTs within 3 hrs and had an average of 3 scans within the first 10d of sTBI. LVVs were quantified by computer assisted, manual volumetric measurements. LVR and midline shift were determined on initial CT to quantify asymmetry. The relationship between the initial LVR and the development of midline shift was assessed.

Sixty percent (15/25) of the patients with high LVR (> 1.8) had 0-5mm midline shift on initial CT, while 40% (15/25) had significant (> 5mm) midline shift. Eight of 15 patients with 0-5mm initial midline shift developed significant midline shift on follow-up scans. For significant midline shift development, an odds ratio of 6.2 ($p < 0.01$) was yielded in the high LVR group compared to patients with low (< 1.8) LVR (7/45 patients developed midline shift).

We propose that LVR captures LVV asymmetry and is not only related to, but predicts midline shift at initial CT examination. Lateral ventricles may have a higher ''compliance'' than midline structures to develope asymmetric brain pathology. This analysis is simple, rapidly accomplished and may allow earlier interventions to minimize midline shift and potentially improve ultimate outcomes.

Key words
outcome, prediction

A3-01

ISOLATED THORACIC SPINAL CORD CONTUSION IN MICE INDUCES COGNITIVE AND EMOTIONAL BEHAVIOR IMPAIRMENTS

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Clinical studies have reported cognitive and emotional deficits after spinal cord injury (SCI). Roth et al. demonstrated that 40–60% of SCI patients show impairment in attention, concentration, memory, learning, and/or problem-solving ability. The cause of the cognitive deficits in SCI patients has been debated, because of potentially confounding factors such as concurrent traumatic brain injury (TBI). Studies that addressed this issue by focusing on SCI cases without signs of TBI have confirmed that these patients also show impairments in cognitive function. Yet, the fact that SCI can cause neurodegeneration in the brain, or that such changes can negatively impact long-term cognitive outcomes or emotional state is still unapreciated by the at-large research and clinical communities. It is known that cognitive/emotional impairments are detrimental to SCI patients not only in their own right but because they can compromise rehabilitation. Here we examined effects of isolated thoracic SCI in mice on cognition, depression, and brain neurodegeneration. To determine whether cognitive/emotional impairments increase as a function of injury severity we exposed mice to sham, mild, moderate, or severe SCI and evaluated performance on a variety of neurobehavioral tests that are less dependent on locomotion. We showed that locomotor function (BMS scores) was reduced in an injury severity manner. Cognitive impairments in the tests of Y-maze, novel objective recognition, and step-down fear-conditioning increased with injury severity at two months post-injury. SCI also caused deficits in emotional behavior as quantified in the sucrose preference, tail suspension, and forced swim test, in a manner dependent on injury severity. Stereological analysis demonstrated significant chronic neuronal loss in the cerebral cortex, thalamus, and hippocampus in the moderate/severe SCI groups. Our data suggest that SCI induces chronic neurodegeneration in important brain regions associated with cognitive decline and depression. Thus, these findings provide the experimental confirmation of clinical evidence suggesting SCI-related cognitive/emotional deficits, considerably revising concepts about the nature of SCI as a focal acute neurodegenerative disorder.

Key words
brain, cognitive impairment, depression, neurodegeneration, spinal cord injury

A3-02

MINIMUM INFORMATION ABOUT A SPINAL CORD INJURY EXPERIMENT (MIASCI): CONCEPTS AND INTEGRATION WITH THE REGENBASE ONTOLOGY

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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, called Minimum Information About an SCI Experiment (MIASCI). Version 1.0 of the MIASCI contains 11 sections: investigator, organism, surgery, perturbagen, cell transplantation, biomaterials, histology, immunohistochemistry, imaging, behavior, and data analysis and statistics. Each section has a number of data elements to be filled in that detail essential metadata about the project, materials and methods. Depending on a particular study, not all sections will apply. 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 standard language. Thus, a parallel effort is underway to develop an ontology about SCI, the RegenBase ontology, and an associated knowledgebase. Expanding RegenBase by incorporating MIASCI concepts facilitates literature curation and knowledge creation. We present MIASCI concepts, show integration with the RegenBase ontology and present different approaches to literature annotation. Querying the RegenBase knowledgebase using the integrated ontology is also illustrated.

Acknowledgments
NINDS NS080145 and NICHD HD057632

Key words
knowledge representation, ontology, reporting standards

A3-03

DATA-DRIVEN DISCOVERY OF SYNDROMIC EFFICACY FOR PRECLINICAL DRUG TRIALS IN CERVICAL SPINAL CORD INJURY

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The growth of preclinical spinal cord injury (SCI) research over the past few decades has produced a huge volume of data, but only few replicable treatments. Often, data presented in published reports represents a fraction of the multiple measures used, varying from laboratory to laboratory. Some of the difficulties in replication may be due to this somewhat fractured approach. We are currently exploring a more integrated big-data approach to yield new insights into recovery from and treatments for experimental SCI, by reevaluating raw data from multiple preclinical trials of cervical SCI. The present study applied a novel multivariate analytic and visualization method known as topological data analysis (TDA) to data from preclinical cervical SCI studies. TDA facilitates rapid data integration, analysis, visualization and interpretation of multiple large datasets simultaneously, promoting rapid data-driven discovery of robust therapeutic effects in large, heterogeneous datasets. As proof-of-concept, data from 6 completed preclinical trials in rats receiving graded cervical SCI (n = 159 rats) with matching functional and histopathological outcomes (m = 340 variables) were mined from the VISION-SCI

database. Data-driven drill-down into subject clusters showing robust multifaceted forelimb recovery revealed enrollment in a placebo-controlled dose response study of soluble tumor necrosis factor receptor-1 (sTNFR1). Correction for robust effects of sTNFR1 in the dataset uncovered significant detrimental effects on tissue sparing from preclinical controlled trials of minocycline and methylprednisolone. Taken together, these results provide a proof-of-concept illustration that TDA and similar big-data analytics may be valuable screening tools of promising preclinical trials prior to replication and translation into clinical trials. Funding: NIH grants NS067092, NS069537, NS038079, NS031193, AG032518, NS079030; Neilsen Foundation 224308; Wings for Life Foundation WFLUS008/12; NYSCoRE CO19772.

Key words
bioinformatics, spinal cord injury, syndromics, topological data analysis

A3-04

TOWARDS PRECLINICAL SENSORY COMMON DATA ELEMENTS IN SPINAL CORD INJURY

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Translational spinal cord injury (SCI) research is challenged by a lack of cross-species common data elements. Additionally, there is not a clear strategy for broad monitoring of both sensory and motor outcomes to screen for maladaptive plasticity, potentially resulting in neuropathic pain. Efforts linking sensory and pain-related outcomes across species are crucial to relate knowledge of mechanism gained in preclinical research to clinical signs and symptoms. To this end, we recently developed the Visualized Syndromic Information and Outcomes for Neurotrauma–SCI (VISION-SCI) database to consolidate sensory, motor, histopathological, and health outcomes within a multicenter, multi-species database. The present study focused on curated sensory outcomes in VISION-SCI, whereby prior work has included motor outcomes. VISION-SCI currently incorporates data from 435 mice, 2225 rats and 59 monkeys. Within the rat population, 59.1% (n = 1315) have motor outcomes, whereas only 10.2% (n = 227) have sensory measures. Of the rats that received sensory testing, 96.5% were also assessed for motor function. Sensory assessments included: forepaw (FP) and hindpaw (HP) von Frey hair (VFH) testing (FP: 56.4%; HP: 95.6%), cold sensitivity (FP: 0%; HP: 7%), segmental (4.8%) and supra-segmental (4.8%) responses to dermatomal VFH stimulation. Despite the predominance of motor outcomes in the database, nearly all studies with sensory function were also assessed for motor recovery, with HP VFH testing being the most common sensory measure collected. The current findings highlight the need for integrating further sensory measures into the database, both from additional studies and species to reveal translational patterns of sensory function. The long term goal of these efforts is to provide an analytical pipeline to pave the way for improved cross-species sensory testing, and accelerate translational research. Funded by: NIH: NS067092, NS079030, NS069537, NS038079, NS031193, AG032518, NS-07291, NS-3-2354; NYSCoRE-CO19772, Wings for Life WFLUS008/12 and Craig H. Neilsen 224308.

Key words
database, sensory system, spinal cord injury, translational research

A3-05

ADVANCED MRI OF THE RAT CERVICAL SPINE FOLLOWING THORACIC CONTUSION SCI

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Magnetic resonance imaging (MRI) is the state of the art approach for assessing tissue viability following spinal cord injury (SCI). However, meaningful imaging metrics are needed to evaluate and monitor injury recovery. Often, the placement of hardware to stabilize the spinal column prohibits followup MRI at the site of injury, but our previous studies demonstrated that remote measures are promising markers of injury and recovery. In this study, cervical spinal cords of rats with a thoracic SCI were imaged using diffusion MRI and T2 to identify remote makers of SCI.

Rats underwent a moderate thoracic injury using a weight-drop device and were imaged on a 9.4T MRI at 2 and 30 days post-injury along with non-injured controls. Diffusion weighted imaging was performed along 2 directions (parallel and perpendicular to the spinal cord axis) using 8 diffusion weighting factors (b-values) up to 3500 mm2/s. T2 imaging was performed with a multiple spin-echo sequence with 42 echos and 6.5 ms echo spacing. DWI was analyzed for diffusivity, anisotropy, and metrics that reflect the non-gaussian behavior of the DWI signal, including kurtosis and bi-exponential fitting. The MERA software package was used to derive quantitative T2 (qT2) data, by calculating the myelin water fraction (MWF), tissue water fraction (TWF), and fat water fraction (FWF) based on the spectrum of signal vs. echo time. Groupwise differences were identified using Student's T-tests.

Using the conventional diffusion MRI analytical model for white matter, no group differences were evident. Likewise, T2 values of the white matter were not significantly different between groups. However, measures of diffusion non-gaussian behavior were significantly elevated at 2 days after SCI compared to the control and day 30 measures. The T2 metrics demonstrated a similar trend of increased FWF at the day 2 timepoint although the change was not significant.

Collectively, the results indicate disrupted water balance and microscopic changes in the cervical cord following a thoracic injury. The advanced MRI measures here may be useful for evaluating and monitoring patient injury and recovery following SCI.

Key words
contusion, diffusion imaging, magnetic resonance imaging, spinal cord injury

A4-01

GFAP FRAGMENT BIOMARKERS AFTER TBI: EVIDENCE FOR ACUTE ASTROCYTE PATHOLOGY

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Astrocytes play important roles in normal brain function and communication. Recent findings indicate that astrocytes may be acutely damaged after ischemic and traumatic brain insults. The objective of this study was to determine the time course of biomarkers of astrocytic damage over the first 24 hours after experimental TBI. Twenty-

one male rats were randomly assigned to either moderate parasagittal fluid percussion or sham injury. Blood serum samples were collected 2 days prior to TBI (baseline) and at 3, 6, and 24 hours after TBI. Single CSF samples were collected from the cisterna magna 24 hours after TBI, followed by euthanasia and brain harvesting for histology. Serum and CSF samples were analyzed for fragmented GFAP and UCH-L1 protein biomarkers using ELISA. Brain histology included Fluoro-jade, hematoxylin and eosin stainings, and GFAP immunostaining. Serum and CSF levels of GFAP were near zero in sham animals. Serum GFAP was significantly elevated to 5.81 ± 1.31 ng/ml ($P < 0.001$, $n = 11$) and 3.16 ± 0.44 ng/ml ($P < 0.05$, $n = 11$) at 3 and 6 hours post TBI, respectively compared to baseline (0.01 ± 0.01 ng/ml, $n = 10$). CSF GFAP at 24 hours post TBI was significantly elevated to 16.14 ± 5.08 ng/ml ($P < 0.01$, $n = 10$) compared to sham (0.03 ± 0.03 ng/ml, $n = 10$). Serum UCH-L1 was significantly elevated at 3 hours post TBI (0.83 ± 0.08 ng/ml, $P < 0.001$, $n = 11$). CSF UCH-L1 at 24 hours post TBI was significantly elevated (26.83 ± 6.31 ng/ml, $P < 0.01$, $n = 10$) compared to sham (6.36 ± 1.35 ng/ml, $P < 0.01$, $n = 10$). Histology revealed characteristic acute neuronal degeneration in the ipsilateral hippocampus and parietal cortex as well as hemorrhage along the corpus callosum and in the parietal cortex. These results suggest that structural damage occurs in astrocytes acutely following TBI. In this model of parasagittal focal contusion, biomarkers of fragmented GFAP appear to be more robustly detected than UCH-L1as an acute marker of brain damage after TBI.

Key words
fluid percussion, pathology, TBI

A4-02

DELAYED CONSCIOUSNESS, SENSORY-MOTOR DEFICITS, AND GFAP LEVELS IN REPEATED CONCUSSIVE IMPACT

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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 the effects of single and repeated mTBI on regaining consciousness, sensory-motor deficits, and GFAP abundance in biofluids. The projectile concussive impact (PCI) model was used to induce mTBI. Anesthetized rats received zero (sham), one (1xPCI) or repeated (2,3 or 4xPCI) impacts separated by 1 h intervals. Righting reflex (RR) and sensory-motor deficits (revised neurobehavioral severity scale, NSS-R) were recorded immediately following the last impact. Serum and CSF GFAP were analyzed by ELISA 1 h after the last concussion. Results showed significant PCI-induced alterations in RR and NSS-R scores following a single PCI ($p < 0.05$ vs. Sham) both of which also showed significant (1.6–1.7 fold) increases in magnitude following the 2nd PCI ($p < 0.05$ vs. 1xPCI). Although both RR and NSS-R remained significantly elevated following a 3rd or 4th PCI ($p < 0.05$ vs. 1xPCI or Sham), no additional ''stepwise'' increases were detected relative to the 2nd impact ($p < 0.05$ vs. 2xPCI). Levels of GFAP in CSF increased to 1.9 ng/mL after a single PCI ($p < 0.05$ vs. sham) and were further increased following repeated concussions with mean levels of 3.9 ng/mL (2xPCI), 2.7 ng/mL (3xPCI) and 7.5 ng/mL (4xPCI) ($p < 0.05$ vs. Sham). Notably, a significant correlation was detected between RR scores and CSF GFAP following 4xPCI ($p < 0.05$). Consistent with this observation, serum GFAP levels analyzed in the 4xPCI group was significantly increased vs. sham (4xPCI = 0.06 ng/mL; Sham = 0.02 ng/mL; $p < 0.05$). Overall, these results suggest that single and repeated PCI lead to neurological impairments that are associated with increased abundance of GFAP in CSF and serum. Funded by CDMRP/DHP Grant W81XWH-12-2-0134.

Key words
concussion, GFAP, mild TBI, serum

A4-03

PLASMA ANTI-GFAP AUTOANTIBODY LEVELS DURING ACUTE AND CHRONIC PHASES OF TBI - A TRACK-TBI PILOT STUDY

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We recently described subacute serum anti-GFAP autoantibody after severe traumatic brain injury (TBI). Here, we expanded our autoantibody study to the multicenter observational study [TRACK-TBI Pilot] cohorts that cover the full spectrum of TBI (GCS 3-15) including acute (< 24 h) plasma samples from 196 TBI patients, and a second cohort of 21 chronic TBI subjects (average 188 days post-injury). We identified that those subjects with self-reported prior TBI and loss of consciousness(LOC) had higher day 1 anti-GFAP autoAb (mean 9.11 arbitrary unit, $n = 43$) when compared to normal controls (mean 2.89; $n = 16$; $p < 0.012$). This data suggest that exposure to TBI could trigger long-lived anti-GFAP autoantibody responses. Importantly, anti-GFAP autoAb levels in plasma collected during the rehabilitation stage after TBI are significantly higher (mean 15.08; $n = 21$) than normal controls, suggesting persisted upregulation of autoimmune response to brain antigen(s) following TBI.

Key words
autoantibody, biomarker, diagnosis, inflammation, outcome

A4-04

BRAIN INJURY SCREENING BY OCULAR ANALYSIS (BISON)

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Traumatic and mild traumatic brain injury (mTBI) can lead to chronic damage and result in permanent disability. mTBI is often undiagnosed at early stages, thereby allowing patients to remain vulnerable to multiple mTBI, a condition that is known to lead to irreversible long-term damage. At present, there are no objective methods to diagnose mTBI, with current diagnosis requiring negative results on a CT scan plus assessment of cognitive and physical symptoms plus behavioral changes. mTBI can lead to alterations in cell functions through biological processes including disruption of the blood-brain barrier (BBB). Similar to the BBB, disruption of the blood eye barrier (BEB) has also been observed and correlated to the severity of brain injury. We hypothesize that biomarkers associated with the autoimmune response initiated by mTBI permeate the BEB through the ciliary vasculature in the eye and result in subclinical changes in protein concentration in the aqueous humor (AH) which can be a direct measure of the damage associated with mTBI. In this study, we analyzed AH protein concentration in two different murine brain injury models including 1) a blast injury model in rats and 2) a repeated mild diffuse injury model in mice. A significantly elevated protein concentration was measured in the AH *ex vivo* ($p < 0.05$) in injured rodents compared to sham controls, supporting our hypothesis. We have also developed and patented a novel optical system which can be used to rapidly (< 30 sec) scan the anterior chamber of a subject's eye to determine ocular inflammation and quantify the concentration of proteins in the AH. A prototype optical system has been tested *in vitro* and *in vivo* in a non-human primate model to determine the ability to measure small changes in AH protein concentrations and is currently being clinically validated. Taken together, these findings may result in an optical device that can rapidly and non-invasively diagnose mTBI by quantifying the change in AH total protein concentration.

Key words
concussion, diagnosis, non-invasive, ocular

A4-05

SERUM MICRORNA SIGNATURES OF CLOSED HEAD INJURY IN MICE: A POTENTIAL BIOMARKER FOR MILD TRAUMATIC BRAIN INJURY

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To date, there is no clinically proven biomarker(s) available for diagnosis of mild traumatic brain injury (mTBI). Circulating microRNAs (miRNAs) are fast emerging as noninvasive diagnostic biomarkers for various diseases because of their specificity and sensitivity. Our main objective of this study was to identify the mTBI altered miRNA signatures in serum to use them as a reliable molecular biomarker. In this study, we used a custom-made weight-drop device to induce a single concussion to the left parietal lobe in mice. Different rod weights (246 and 333 g) and fall heights (2 and 3 cm) were used to create four injury groups. Neurobehavioral Severity Scale-revised, open field activity and acoustic startle response were studied at 24 hours post injury. MiRNA expression profiling for serum collected at 3 hours post injury were performed using TaqMan MicroRNA Array cards. Neurobehavioral tests showed transient behavioral changes at 24 hours post injury. MiRNA profiling in serum showed thirteen common miRNAs between the four injury groups. *In silico* analysis indicated most of the thirteen miRNAs to be either of brain origin or predicted to be involved in TBI pathophysiology. Network 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. Brain related serum miRNAs- miR-199-3p, miR-214 and miR-376a were validated. Altered serum miRNAs expression at 3 hours post injury showed correlation with TBI pathophysiology indicating their potential as a novel molecular biomarker for mTBI. (Opinions expressed here are those of authors and does not reflect views of USUHS, DMRDP or BITS Pilani).

Key words
mild TBI, serum microRNAs, weight drop model

A4-06

MICROTUBULE-ASSOCIATED PROTEIN 2 (MAP2) CSF BIOKINETIC CHARACTERISTICS ARE ASSOCIATED WITH POOR OUTCOMES IN SEVERE TBI PATIENTS

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MAP2 is a promising new candidate biomarker of dendritic injury; however, most studies identify one point in time to determine associations with outcomes. This study assesses the relationship between the exposure and kinetic metrics of MAP2 in cerebral spinal fluid (CSF) over time and clinical outcomes. This prospective observational study was conducted in patients with severe TBI ($GCS \leq 8$) requiring a ventriculostomy. CSF samples were obtained every 6 hours on day 1, then every 24 hours for up to 10 days post injury and analyzed for multiple biomarkers using an ELISA; with MAP2 showing strong correlations. Biokinetic parameters evaluated include area under the curve (AUC), maximum concentrations (Cmax), time to maximum concentration(Tmax), mean residence time (MRT) and half-life. Of the 120 patients with kinetic metric results, 92 had outcome data available for analysis. There were significant correlations between increasing median AUC and Rotterdam scores predicting risk of mortality ($p < 0.001$). When Marshall Classification was dichotomized into I-II versus III-VI, the median AUC and Cmax were significantly higher in the III-VI group ($p < 0.001$). Among patients with Marshall Classification I-II versus III-IV, median AUCs were 116 vs 475 ng/ml*hr($p = 0.001$) and median Cmax was 2.4 vs 9.2 ng/ml($p = 0.001$). The median AUC for GOSe at 6 months in those with favorable versus unfavorable outcome were 82 vs 323 ng/ml*hr ($p = 0.007$), the median Cmax was 2.4 vs 8.7 ng/ml($p = 0.005$), the median MRT was 52 vs 69 hr ($p = 0.056$). MAP2 exposure and biomarker kinetic metrics over the 10 day study time period show significant correlations with prognostic imaging classifications and poor clinical outcomes in severe TBI patients.

Key words
biomarker, MAP2, TBI

A4-07

DETERMINING THE FEASIBILITY OF USING HEART-RATE VARIABILITY FOR THE IDENTIFICATION OF MILD TBI IN ASYMPTOMATIC PARTICIPANTS

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Many who experience a mild traumatic brain injury (mTBI) have transient symptoms. However, a subset of the mTBI population will present symptoms weeks, months, or years after the event has occurred. As a result, health-care providers and even the injured person may not identify the mTBI incident as being the cause of their current symptoms. Therefore, it is crucial that an accurate method of assessing mTBI in the asymptomatic individual be developed. If left untreated, individuals with chronic mTBI sub-threshold deficiencies may be at higher risk of developing serious neurological and psychiatric disorders. Heart-rate variability (HRV), the variation in time intervals between heartbeats, reflects the sympathetic and parasympathetic balance of the autonomic nervous system. We hypothesized that HRV measures can be used to identify the population of asymptomatic mTBI individuals from a healthy control population months following the TBI incident. In this study, five mTBI participants and 14 controls participated in an IRB approved research protocol consisting of two sessions, each six months apart. Subjects were presented with a battery of cognitive tasks. Electrocardiogram (ECG) data was acquired and processed to obtain measures of heart rate and HRV. A diagnostic, self-report assessment for depression, the PHQ-9, was administered as part of our behavioral assessments. The PHQ-9 showed no significant difference in depression measures between the controls and mTBI subjects. However, results for the HRV measure suggest a clear difference with controls and mTBI subjects between sessions as determined by repeated measures ANOVA ($F=6.872$, $p=0.022$). These results suggest that HRV is an objective measure of mTBI impairment during task performance even in the asymptomatic mTBI victim. Identification of such individuals via HRV assessment may be a useful tool in longitudinal tracking of mTBI recovery and response to interventions targeted at restoration of autonomic function. This research is on-going and updated results will be presented.

Key words
electrocardiogram, heart rate variability, traumatic brain injury

A4-08

IMMUNO-CHAIN REACTION: A NOVEL ULTRASENSITIVE ASSAY FOR RAPID TRIAGING OF BRAIN INJURY

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Rapid, real-time triaging of mild traumatic brain injury (mTBI) or concussion with a simple pinprick blood test at the sideline or at the point of injury necessitates measuring protein biomarker candidates at fM concentrations. The inherent characteristics of many immunoassay methods preclude the development of a viable blood test based on them. To overcome this hurdle, we report here a novel immunoassay technology based on Immuno-Chain Reaction (ICR), which successfully demonstrated the assay of glial fibrillary acidic protein (GFAP), a leading biomarker of gliosis in the acute phase of TBI, in the 0-100 pg/mL range in five minutes using less than 3 μl human mTBI serum. Duplex detection of GFAP and bovine IgG spiked in human serum has also been demonstrated. Results indicate that, using spiked bovine IgG as an internal standard, it is possible to triage mTBI/concussion based on a specific cutoff. Day-to-day reproducibility was demonstrated for the detection of 10 pg/mL GFAP in serum. The feasibility of ICR assay in banked CSF samples and detection of autoantibodies have also been verified. ICR achieves an ultralow limit of detection through amplification brought about by a PCR-like, immuno-displacement chain reaction. Because all the reagents are pre-immobilized, ICR-based devices do not require any reagent storage, pumps or valves or an associated control system. This greatly simplified instrumentation requires only a control board for signal readout and makes the device affordable, reliable and user-friendly. The ICR assay is inherently ideal for rapid detection of protein biomarkers in ultralow concentrations and has great potential for triaging concussion and other emergency or low resource indications.

Key words
biomarker, glial fibrillary acidic protein, immunoassay, mild traumatic brain injury, triage

A4-09

HUMAN ASTROGLIAL MARKERS ARE DEFINED BY RELEASE MECHANISMS AND ARE ELEVATED IN TBI PATIENTS' CSF AND SERUM

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There is an unmet need for chemical surrogate markers of traumatic brain injury (TBI). Cellular consequences of mechanical trauma are poorly understood. The goals of this study were to define the release parameters of a new set of astroglial enriched proteins in a controlled *in vitro* injury model and measure their elevation in TBI patient's CSF and serum. Densitometric immunoblotting analyses and quantitative mass spectrometry measurements using multiple reaction monitoring (MRM) of the fluid samples were established. Percent human astrocytes with membrane permeability and cell death were quantitated using dye uptake imaging. Marker release levels were related to trauma severity and analyzed over time postinjury. Abrupt pressure stretching caused acute membrane permeability (30 min postinjury) whereas severity-dependent cell death was seen by 48 hours postinjury. Astrocyte-enriched markers were released acutely and increased with severity and over time postinjury. TBI patients' CSF levels of these astroglial markers were elevated compared to controls with highest amounts on injury day and secondary peaks over time postinjury. Correlation analyses showed covariant release pattern among these astroglial proteins. Selected astroglia markers were detected in TBI patients' serum indicating blood brain barrier passage. Thus, our controlled *in vitro* model defined human astrocyte's trauma responses and release kinetics for a new set of astroglial proteins that we validated in TBI patient's CSF and serum. Release from mechanoporated cells prior to significant cell death distinguished these proteins from cell death inflicted trauma markers. In conclusion, we provide a panel of human astrocyte-derived biomarker candidates useful for acute diagnosis and monitoring the progressive pathophysiology of TBI patients with varying severities.

Key words
CSF, *in vitro* model, proteomics, serum

A4-10

GFAP AUTOANTIBODY DEVELOPMENTAL TRAJECTORIES AFTER TBI: CHARACTERIZATION AND ASSOCIATIONS WITH INFLAMMATORY MARKERS

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Following blood brain barrier disruption after traumatic brain injury (TBI), brain proteins enter the peripheral circulatory system where they may trigger an immune response. Glial fibrillary acidic protein (GFAP) is expressed within the central nervous system, and levels are elevated following TBI. Recently, our work identified the presence of autoantibodies (AutoAb) toward GFAP following TBI. Also, IL-7 is important for immune cell development and is implicated in autoimmune neurodegenerative diseases like multiple sclerosis. Thus, we explored 1) temporal GFAP autoAb development after severe TBI, 2) relationships between GFAP AutoAb longitudinal profiles and early cerebrospinal fluid (CSF) GFAP levels, and 3) concurrent IL-7 associations with GFAP autoAb production among TBI survivors. Acute CSF and serum, along with chronic serum samples (up to 6 months post-injury) were obtained from 36 adults with TBI; CSF and serum samples were obtained from 20 controls. Samples were assayed to measure CSF GFAP and GFAP autoAb, and serum GFAP autoAb and IL-7 levels. Absolute autoAb level and fold-change from acute baseline GFAP autoAb were compared between TBI cases and controls and to IL-7 levels. We used group-based trajectory analysis to identify two distinct temporal GFAP autoAb profiles showing significantly different GFAP AutoAb levels across the sampling period. GFAP AutoAb was higher in cases versus controls at all chronic time-points ($p < 0.005$). Acute GFAP AutoAb correlated with chronic GFAP AutoAb levels ($p < 0.05$), and serum GFAP autoAb correlated with serum IL-7 at multiple chronic time-points. Additionally, IL-7 levels differed between trajectory groups at multiple time-points ($p < 0.05$). This is the first study to describe temporal GFAP autoAb profiles following TBI and to implicate inflammation, particularly IL-7, as a possible contributor to autoimmune response development post-TBI.

CDCR49 CCR323155; DODW81XWH-071-0701

Key words
auto-antibody, cytokine, GFAP, traumatic brain injury

A4-11

METABOLOMIC ANALYSIS OF BIOFLUIDS FROM PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY: INFLUENCE OF CEREBRAL LACTATE SUPPLEMENTATION

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We have previously shown that the human brain can utilize lactate as a fuel after severe traumatic brain injury (TBI). We hypothesize that a detailed metabolomic analysis of patient body fluids during lactate infusion would reveal important improvements in cerebral metabolism.

Cerebral spinal fluid (CSF), arterial and jugular blood were collected from 6 severely injured TBI patients (5 male, 1 female; age 26.5 ± 14.0, admission GCS 6.8 ± 3.4) at baseline and 3 hours after the start of sodium l-lactate infusion (90 mg/min). Samples were centrifuged and frozen at -80^{o} C and shipped to Metabolon (Research Triangle, NC). Biofluid analysis included GC/MS and UPLC-MS/MS. Statistical analysis included significance tests and classification analysis. For pair-wise comparisons, Welch's t-tests and/or Wilcoxon's rank sum tests were used on the R platform.

Analysis of CSF and arterial and jugular plasma identified 197 and 335 biochemicals, respectively. Statistical analysis of CSF showed statistical significance ($p < 0.05$) and trends ($p < 0.1$) in 5 and 9 metabolites, respectively. Plasma samples showed statistical significance and trends in 22 and 19 metabolites, respectively. CSF pathway analysis detected trends towards reduced glycolysis and pentose phosphate metabolite levels as a result of lactate infusion. Additionally trends of 1-1.2 fold increases in TCA cycle metabolites were also seen. TCA cycle differences were also observed in arterial and jugular plasma. Interestingly, fructose levels were increased in arterial and decreased in jugular plasma indicating a cerebral uptake of this sugar molecule.

These data support the notion that lactate nutritional supplementation can significantly affect cerebral metabolism. Positive effects on TCA metabolism indicate that lactate can be beneficial to the injured brain. Although small in size, this study demonstrates the utility of metabolomic analysis of biofluids from TBI patients.

Acknowledgments
This research was supported by the UCLA Brain Injury Research Center, and NINDS 1P01NS058489-01.

Key words
cerebral metabolism, metabolomics, recovery of function

A4-12

C-REACTIVE PROTEIN AUGMENTS THE DIAGNOSTIC VALUE OF GLIAL FIBRILLARY ACIDIC PROTEIN IN DETECTING ACUTE CT INTRACRANIAL PATHOLOGY

Yue, J.K.[1], Cooper, S.R.[1], Diaz-Arrastia, R.[2], Wang, K.K.[3], Sorani, M.D.[1], Lingsma, H.F.[4], Yuh, E.L.[1], Mukherjee, P.[1], Valadka, A.B.[5], Gordon, W.A.[6], Okonkwo, D.O.[7], Manley, G.T.[1]
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Glial fibrillary acidic protein (GFAP) is released following parenchymal brain injury and has been studied as a potential diagnostic biomarker. The liver-derived C-reactive protein (CRP) is a stable plasma marker and its production increases following acute trauma. We examined concurrent plasma GFAP and CRP in a cohort of 61 patients enrolled in the multicenter observational Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) Pilot Study. Blood samples were collected < 24 hours of acute TBI and analyzed. In addition to GFAP, CRP was identified as a potential useful TBI biomarker. In patients with intracranial lesions on brain CT (+CT),

GFAP (-CT: 0.1 ng/ml (IQR 0.0-1.7), n = 31; + CT: 2.0 ng/ml (0.4-3.3), n = 30) and CRP (-CT: 0.5 ug/ml (IQR 0.3-1.7), + CT: 27.5 ug/ml (IQR 6.3-50.0)) were significantly higher ($p < 0.0001$, Mann-Whitney U). Logistic regression of the combined GFAP-CRP model (GFAP Odds Ratio (OR) 12.9, CRP OR 1.6, Nagelkerke R^2 (NR^2) 0.87, $p < 0.01$) performed better than GFAP (OR 7.5, NR^2 0.54, $p < 0.01$) or CRP (OR 1.5, NR^2 0.70, $p < 0.01$) alone in detecting + CT. Likewise the receiver-operating characteristic (ROC) curve of the combined model had a higher area under the curve (AUC) of 0.986 ($p < 0.0001$) compared to GFAP (AUC 0.891) or CRP (AUC 0.931) individually. Our data suggests that GFAP and CRP are part of distinct physiological cascades in response to injury (Pearson's r 0.272, $p = 0.034$), and supports the development of a combined panel of biomarkers to improve acute TBI detection.

Key words
clinical trial, human studies, traumatic brain injury

A4-13

PLASMA LIPIDOMIC TBI BIOMARKER PROFILES - TRANSLATION FROM MOUSE TO HUMAN

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Traumatic brain injury (TBI), in particular mild TBI (mTBI) is a major problem for military and civilian populations. An objective panel of TBI biomarkers and related conditions would enable appropriate medical management, may indicate ongoing pathogenic processes, provide guidance in therapeutic development, and could be used to monitor outcome and response to treatment. We have developed a mouse model of single and repetitive mTBI that shows progressive neuroflammation and neurobehavioral changes, characterized through to 2 years post injury. One next step is to identify potential peripheral biomarkers of injury. Phospholipids (PLs) such as phosphatidylcholine (PC) and sphingomyelin (SM), play a prominent role in neuronal processes including neurotransmitter release, neurite outgrowth and synaptogenesis, and brain lipid metabolism is disrupted in our preclinical TBI models. We have used our lipidomic platform (in-source collision induced dissociation (sCID) with full scan liquid chromatography/MS (LC/MS)) to generate a temporal profile of plasma lipidomic changes in our mouse model. Plasma profiling demonstrates significant TBI-dependent changes in lipid profiles that persist years after the injury, including significant increases in PC and SM. To determine the clinical relevance of these findings we will correlate plasma lipidomic changes with brain lipidomic changes in this model, but we are also validating our findings by investigating plasma lipid profiles in human TBI populations. Our pilot human data, from lipidomic profiling in a cohort of soldiers pre and post-deployment, show plasma lipid changes in those with a documented TBI that are consistent with those seen in the mouse model.

Funding: CDMRP funding (W81XWH-10-1-0759), and VA Merit funding; MOMRP funding and Roskamp Foundation.

Key words
lipidomic, military, plasma

A4-14

MULTI-ANALYTE BIOMARKER PANEL PREDICTS FUNCTIONAL OUTCOME 6 MONTHS AFTER TRAUMATIC BRAIN INJURY

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Blood biomarkers show promise as tools to identify mild TBI (mTBI) patients at risk of long-term functional deficits, but given the heterogeneity of mTBI, it is unlikely that a single biomarker will have sufficient sensitivity and specificity to be useful. We ran a multi-analyte panel of 87 biomarkers (HumanMap v.2.0, MyriadRBM, Austin, Texas) on a cohort of 62 participants in the TRACK-TBI Pilot Study. 90% had mTBI (GCS 13-15) and 50% had normal cranial CT. Plasma was collected <24 hours after injury and stored frozen until assayed. We considered only biomarkers where >90% of samples provided values higher than the Lower Limit of Quantitation. Biomarkers with >30% of TBI samples outside (either higher or lower) than the 95% confidence interval for healthy controls were analyzed using binary logistic regression, with full recovery 6 months after injury (GOSE 8) as the dependent variable. 20 biomarkers from the HumanMap v.2.0 panel were included in the anlysis. A model including only age, admission GCS, and CT findings correctly classified only 72.1% of cases, and explained only a trivial fraction of variance (Cox and Snell R^2 (CSR^2) = 0.020, Nagelkerke R^2 (NR^2) = 0.029). Adding UCHL-1 and GFAP to the model did not significantly improve the model (classification 72.9%, $CSR^2 = 0.122$, $NR^2 = 0.174$). Adding the 20 HumanMap v.2.0 biomarkers substantially improved the model (classification 100%, $CSR^2 = 0.690$, $NR^2 = 1.00$). These findings are preliminary and must be replicated in a larger, independent cohort, but indicate that multiplex assays of biomarkers are potentially useful for identifying patients with mTBI who fail to make a complete recovery.

Key words
GOSE, Luminex, multiplex immunoassay

A4-15

EXTRACELLULAR MATRIX BIOMARKERS ARE SEVERITY DEPENDENT AND REGIONAL SPECIFIC IN EXPERIMENTAL DIFFUSE BRAIN INJURY

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The extracellular matrix (ECM) provides structural support for neuronal, glial and vascular components of the brain, particularly through

glycoproteins. The ECM 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 then 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, and blood were collected at 1, 3, 7 and 14 days post-injury. All samples were quantified by western blot for the glycoproteins: reelin, fibronectin, laminin, and tenascin-c. Band intensities were normalized to sham and relative to β-actin. The lateral hippocampus, containing area CA3, was most sensitive to injury-induced change in ECM protein levels. In this region, reelin did not show significant changes in the primary band of interest (415 kDa) over time post-injury. Fibronectin increased over 1 day and 3 days post-injury at mild and moderate severity, returning to sham levels by 7 days post-injury. Laminin levels increased at 7 days post-injury for the moderate severity. Tenascin-c was differentially affected over time post-injury compared to other ECM components. The ECM remains a potential source of biomarkers to distinguish ongoing processes of circuit dismantling and repair in the wake of diffuse TBI, based on the expression profile of ECM molecules. Further investigation into breakdown products and penetrance into blood is needed.

Funding: Translational Collaboration Grant from PCH and ASU

Key words
biomarker, diffuse brain injury, extra cellular matrix, glycoproteins

A4-16

IDENTIFICATION OF A PUTATIVE PANEL OF SERUM MICRORNAS FOR DIAGNOSIS OF HUMAN TRAUMATIC BRAIN INJURY

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MicroRNAs (MiRNAs) are small endogenous RNA molecules and have emerged as novel serum diagnostic biomarkers for many diseases due to their stability and detection at minute quantities. In this study, we have putatively identified a novel serum miRNA signature in human serum samples of mild and severe TBI, which can be used for diagnosis of mild TBI (mTBI).

Human serum samples (n = 8 each) of mTBI, severe TBI, orthopedic injury and healthy controls were used which were collected within 24 hr of injury. MiRNA profiling was done using taqman low density array platform followed by data analysis.

The real time PCR data for the mTBI, severe TBI and orthopedic injury was normalized to the control samples. Our analysis showed that 89, 82 and 116 miRNAs were significantly modulated in serum samples of mild, severe and orthopedic injury groups respectively. To identify ''TBI-specific'' miRNAs, TBI groups were compared to orthopedic injury group which showed up-regulation of 13 and 17 miRNAs in mTBI and severe TBI groups. Among these, a signature of 5 miRNAs was found to be present in both mTBI and severe TBI cases only. Comparison of these 5 miRNAs with serum miRNA profiles of animal TBI models in our laboratory revealed similar miRNAs between human and animal serum post injury.

MiRNAs profiles of orthopedic injury showed an overlap with many miRNAs expressed in TBI samples. By subtraction, we identified a subset of five unique miRNAs which were only present in serum from mild and severe TBI subjects. These five miRNAs are reported for the first time as diagnostic markers of mTBI and severe TBI.

The views presented here are of the authors and should not be construed as that of UF, ORMC or USUHS.

Key words
biomarker, microRNA, mild TBI, serum

A4-17

LIPIDOMIC PROFILING OF SERUM FOR THE DEVELOPMENT OF BLOOD BASED BIOMARKERS FOR TRAUMATIC BRAIN INJURY

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Biomarkers are a promising diagnostic adjunct for TBI, yet there are no candidate blood and/or cerebrospinal fluid biomarkers that have translated to clinical use. The vast majority of the proposed biomarkers have been identified by targeting astroglial and neuronal proteins that are affected by secondary injury. Changes in the lipid profile of blood following TBI have not been well studied, despite evidence of membrane phospholipid degradation and the release of polyunsaturated fatty acids following TBI. We use an untargeted approach to study the global lipidomic profile of serum utilizing high resolution liquid chromatography mass spectrometry (LC-MS) in rats injured by the controlled cortical impact (CCI) model (n = 23) at 3 and 7 days post-CCI. LCMS run in positive mode identified 870 features, and an iterative algorithm was used to identify the features most indicative of injury. Initial results show that concentration changes in a panel of 8 lipids on the mass range 524 to 835 can differentiate injured samples (n = 14) from sham and naïve control (n = 9) with 100% specificity and 93% sensitivity. The exact mass of each lipid matches an existing phosphatidylcholine structure within 10 ppm error, allowing for the assignment of elemental formulae. Tandem MS supports this class identification as evidenced by the presence of a phosphatidylcholine headgroup upon fragmentation. These preliminary data gives support to the lipidomic approach to identifying TBI biomarkers, warranting further study. Novel biomarker panels for TBI diagnosis should consider inclusion of lipid-based molecules. (NIH 5T32EB006343-05).

Key words
lipid, mass spectrometry, phospholipid

A5-01

CLOSED HEAD INJURY ENHANCES COGNITIVE DEFICITS AND DISRUPTS THE RESOLUTION OF THE GLIA RESPONSE IN AN ALZHEIMER'S MOUSE MODEL

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Epidemiological studies have found a self-reported history of head injury is associated with earlier onset, and increased Alzheimer's

disease (AD) pathological and cognitive changes. Notwithstanding the limitations inherent in retrospective studies, the evidence suggests that head injury is an important risk factor for the subsequent development of dementia. We hypothesized that a single closed head injury would accelerate the onset of cognitive impairment in a mouse model of AD. APP/PS1 KI (AD) mice and their wild-type (WT) littermates received a closed head injury (CHI) at 8 months of age, prior to cognitive deficits in the AD mice. Cognitive changes were measured at 1 mo post injury by radial arm water maze (RAWM). CHI AD mice were found to have a significant impairment in RAWM compared to sham AD mice and CHI WT mice. Currently, little is known about how a single head injury accelerates onset of AD; yet, clinically, neuroinflammation has been found to be chronically elevated after a single head injury suggesting a failure to resolve the healing process. As neuroinflammation can affect AD neuropathology and cognitive impairment, we tested whether an altered inflammatory response following a traumatic brain injury might be a contributing factor. Temporal changes in amyloid and glial responses were measured at 9 h, 24 h, 7 d, and 2 mo post injury. Unexpectedly we found in the injured AD mice that the temporal astrocyte and cytokine/chemokine response was delayed compared to injured WT mice. However, once activated, the glial injury response (cytokine/chemokines and microglia/astrocyte markers) in the AD mice failed to resolve compared to the WT injured mice. In agreement with clinical findings, our experimental model suggests that a single head injury can accelerate cognitive impairment, and that the mechanism may involve an unresolved neuroinflammatory response in injured AD mice. Future studies are ongoing to test this possibility.

Key words
Alzheimer's disease, astrocyte, closed head injury, cytokine, microglia, radial arm water maze

A5-02

BLAST EXPOSURE IMPAIRS THE BRAIN'S ABILITY TO MODULATE SENSITIVITY TO SENSORY INFORMATION: EVIDENCE FROM THE VETERAN POPULATION

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Based upon the constellation of chronic multisensory and cognitive problems frequently exhibited by Veterans exposed to high-intensity blast waves, we hypothesized that blast exposure may damage the neural networks involved in filtering sensory information.

We assessed the auditory filtering characteristics of a group of blast-exposed Veterans and non-blast-exposed control participants using self-report, behavioral, and electrophysiological measures. Self-report indices included the Neurobehavioral Symptom Inventory (NSI), the Sensory Gating Inventory (SGI), and the Functional Hearing Questionnaire (FHQ). Behavioral measures included speech comprehension, the Comprehensive Trail Making Test (CTMT), and the Stroop Color-and-Word test. Objective measures of auditory filtering included the auditory P300 oddball paradigm, the sensory gating paradigm, the intensity dependence of auditory evoked potentials (IDAEP), and habituation and prepulse inhibition of the acoustic startle response (ASR).

Preliminary results indicate that blast-exposed Veterans have higher rates of perceived sensory and cognitive dysfunction compared to control participants as revealed by significantly higher scores on the NBSI, SGI, and FHQ. Stroop testing revealed that blast-exposed Veterans were slower to respond on all portions of the test. Blast-exposed Veterans also scored below average on portions of the CTMT requiring attention to specific visual stimuli while ignoring visual distractors. Electrophysiological test measures demonstrated poor habituation to ASR stimuli, reduced sensory gating measured at both pre- and post-attention levels of processing, and markedly reduced responses to the auditory P300 oddball stimulus compared to control participants.

Poor habituation to ASR stimuli, reduced sensory gating, and below average scores on the CTMT all indicate an inability to inhibit responses to irrelevant stimuli in blast-exposed Veterans, while reduced P300 responses reveal reduced capacity for neural response to novel or rare stimuli. Overall, these results indicate that blast exposure reduces one's ability to appropriately respond to novel stimuli while ignoring distracting stimuli, a condition which likely contributes to downstream cognitive issues.

Key words
auditory, blast exposure, sensory processing, traumatic brain injury, veterans

A5-03

APPLICATION OF AN ACTIVE AVOIDANCE TASK IN DETECTING COGNITIVE DEFICITS FOLLOWING PENETRATING BALLISTIC-LIKE BRAIN INJURY

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In this study we used a modified active avoidance (AA) task to characterize cognitive deficits associated with emotional distress in rats following penetrating ballistic-like brain injury (PBBI). The AA device consists of a revolving arena covered by shock pads that are electrically charged only when rotating into a designated shock zone (SZ) (1/6 of the arena area). The goal of AA is for animals to learn to use environmental cues to avoid entering the SZ. Anaesthetized rats received PBBI (5% or 10% injury severity) or sham surgery. At 7 days post-injury (DPI), each rat was habituated to the arena (10-min) with the SZ turned off. On post-injury days 8 and 9, the rats received two avoidance acquisition trials per day (5 min/trial; 1 h ITI) in the revolving arena with the SZ turned on. At 10 DPI, the SZ was shifted 180° and the animals were exposed to a reversal learning test (4 trials; 5 min/trial; 1 h ITI). No significant injury-induced alterations in spontaneous locomotor behavior were detected during the habituation trial. However, results of AA acquisition trials and reversal tasks revealed significant injury-severity dependent deficits. More specifically, compared to sham controls, PBBI animals made more entries into the SZ (Sham: 1.9 ± 1.1; 5% PBBI: 3.5 ± 2.1; 10% PBBI: 9.9 ± 2.9) and displayed significantly longer escape latencies (Sham: 2.1 ± 1.5s; 5% PBBI 10.9 ± 8.7s, 10% PBBI: 22.9 ± 8.8s) on the last day of acquisition. Similar deficits associated with injury severity were also detected on the reversal test for entry frequency: (Sham: 2.0 ± 0.8; 5% PBBI: 7.0 ± 3.1; 10% PBBI: 10.8 ± 3.6), and escape latency (Sham: 20.6 ± 6.8s; 5% PBBI: 31.8 ± 6.9s; 10% PBBI: 42.0 ± 12.6s). Overall, these results indicate that the AA task provides a sensitive measure for detecting cognitive dysfunction in the PBBI model. While ongoing work will determine whether this task would be sensitive to mild TBI, the current results suggest this may provide a useful measure for detecting efficacy of promising pharmacotherapeutics in the PBBI model.

Key words
active avoidance task, learning and memory, penetrating ballistic-like brain injury

A5-04

THE INCIDENCE OF TRAUMATIC BRAIN INJURY IN THE COUNTY OF KAINUU, FINLAND: THE KAINUU TBI COHORT

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Aim of the study is to provide up-to-date retrospective information on the incidence rate, demography and etiology, and evaluate the state of clinical practice in adults (>16 yrs) with traumatic brain injury (TBI).

All patients with an ICD-10 diagnostic code indicating TBI or a high probability of TBI were collected from the medical files of Kainuu Central Hospital during 2004–12 (population 85000). Demographic features, etiology, and clinical findings for the diagnosis of TBI were reviewed.

We identified 2300 potential TBI patients of which the first 460 were reviewed. Of them, 23 patients were excluded because of TBI before year 2004, 70 patients were 16 or less by age, and further 49 patients were living outside the region of Kainuu. Of the remaining 318 patients, 96 were diagnosed non-TBI and 59 uncertain TBI. The remaining 163 had definite TBI (59% males, 41% females) and make up the final study sample. The annual incidence of TBI was 107/100000 inhabitants, calculated, on the basis of the sample, from potential TBI patients in the study population. Falls were the leading cause of TBI. Seven percent of 163 patients were admitted to the intensive care unit, 58% to an in-patient ward, and the remaining 35% to an out-patient ward. Three percent of the patients were unconscious at admission to hospital, 9% had lowered level of consciousness, and the remaining 88% were fully conscious. Disorientation, headache, and nausea were symptoms of 40% of patients, and evidence of unconsciousness or amnesia was found in 35% of patients. Acute CT scan was acquired of 48% of patients; one third had acute TBI related findings.

The observed incidence of TBI was relatively low compared to previous epidemiologic studies suggesting that many TBIs remain undiagnosed.

Key words
cohort, epidemiology, incidence, retrospective, traumatic brain injury

A5-05

OBSERVED DIFFERENCES BETWEEN ATHLETES WITH AND WITHOUT ADD AT BASELINE AND ACUTE POST-CONCUSSION ASSESSMENT

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Sport-related concussion has been increasingly studied as its importance as a public health concern has grown. Computerized neuropsychological testing is an important component in concussion management. In this study, we examined baseline and acute post-injury performance of concussed athletes who reported a history of Attention Deficit Disorder (ADD), in comparison to a matched sample who did not report the diagnosis.

Subject data was acquired from a larger de-identified database. Included were athletes aged 14–18 who had completed baseline and post-injury computerized neuropsychological testing. A group of athletes who reported a history of ADD were acquired (n1 = 970), then an age-matched comparison group was extracted (n2 = 970). Outcome measures included the Verbal Memory, Visual Memory, Visual Motor Speed, and Reaction Time composites from the ImPACT test, from the baseline and acute post-injury (< 7 days) assessments.

1940 subjects were included in the analysis, 75% were male, and mean age was 15.65. MANOVA revealed significant differences across all composites when comparing baseline ($F = 26.06$; $p < .001$) and post-injury ($F = 72.03$, $p < .001$) scores, with the ADD group performing worse. Both groups saw expected declines from baseline for all composites ($p < 0.05$) following injury. The interaction between time and ADD diagnosis was also significant ($F = 3.29$, $p < .05$).

The findings underscore the importance of having a valid baseline for all athletes prior to participation in a contact sport. Additionally, given observed differences in group performances for athletes with ADD, as well as the notion that this population may demonstrate greater variability in baseline performance, it is essential to obtain baseline testing for these and other special populations. Both groups showed expected declines in performance following concussion.

Key words
ADD, computerized testing, concussion

B1-01

EVALUATION OF THE MILITARY FUNCTIONAL ASSESSMENT PROGRAM: ASSESSMENT OF THE CONSTRUCT VALIDITY USING ARCHIVED CLINICAL DATA

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There are several important factors to consider when making a decision to return a Soldier to duty after a traumatic brain injury (TBI). If returned prematurely, there is an increased risk for not only second impact syndrome during the acute phase of the injury, but also permanent changes from repetitive concussions. Thus, there is a critical need for a set of return-to-duty (RTD) assessment criteria that encompasses the spectrum of injury and disease experienced by U.S. Soldiers, particularly TBI. Fort Campbell National Intrepid Center of Excellence-Intrepid Satellite III has developed and begun implementing the Military Functional Assessment Program (MFAP), which uses face-valid military tasks paired with clinical assessments to help determine a Soldier's readiness for active duty.

The objective of this study was to provide evidence-based standards that may eventually serve as criteria for operational competence and performance of a Soldier after injury. Specifically, the relationships between clinical assessments and the MFAP's novel military-specific tasks were evaluated. Exploratory analyses (including non-parametric tests and Spearman's rank correlations) were conducted on an archived database of 79 patients with TBI who participated in the MFAP.

Several of the military operational assessment tasks correlated significantly with clinical measures of vestibular function, psychological well-being, and cognitive function. Soldiers who passed the MFAP differed significantly from Soldiers who did not pass the MFAP on clinical function, self-reported occupational performance, psychological well-being, and Military Acute Concussion Evaluation (MACE) scores.

This study demonstrated an initial convergent validity between MFAP tasks and clinical assessment scores. The MFAP shows promise for augmenting decision making related to RTD and Soldier skills. These findings support additional research efforts to determine the effectiveness of this program in predicting RTD success.

Key words
fitness-for-duty, military, return-to-duty

B1-02

BARRIERS TO RECOVERY AFTER CONCUSSION

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This study examines factors influencing recovery from concussion and investigates the correlation between duration and quality of prescribed rest and recovery time. The prescribed treatment for a concussion is physical and cognitive rest. Both physicians and patients struggle with defining the prescription of "rest" and compliance. Few other studies have evaluated the optimal amount and type of prescribed rest necessary to influence recovery. Any patient between the ages 10 and 50 years diagnosed with concussion was asked to complete a questionnaire regarding their activity during their recovery period. A total of 170 patients were asked to participate between November 2011 and September 2013 and 34 had completed it by this time. Football (29%) was the most common sport played, followed by baseball (13%) and soccer (13%). On average, females had a longer recovery time compared to males (125 versus 86 days, respectively) and all females had recovery periods of 14 days or longer. Mechanism of injury was associated with longer recovery period. Those who hit their head on stationary or moving objects were more likely to have recovery periods 14 days or longer compared to collision injuries ($p = 0.015$ and 0.004, respectively). While many activities were associated with longer average recovery times, only reading ($p = 0.024$) and listening to audio books, talk radio, or podcasts ($p = 0.003$) were statistically significant. Patients who had previous concussions had a recovery length nearly four times longer than first time concussion patients ($p = 0.011$). Gender, mechanism of injury, pastimes during recovery and concussion history all have a significant impact on concussion recovery time. Females have a more difficult time recovering than males. The mechanism of injury influences the duration of symptoms, possibly related to the degree of rotational acceleration the brain is subject to. Cumulative injury from concussions is of concern.

Key words
activity, barriers, recovery, screen time

B1-03

EFFECTS OF DUAL MODE NON INVASIVE BRAIN STIMULATION ON MOTOR FUNCTION IN PATIENTS WITH CHRONIC TRAUMATIC BRAIN INJURY

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Transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS), when provided to brain injured patients in combination with motor training, enhances therapeutic efficacy and motor function. However, a majority of studies only examined a stroke patient.

The authors investigated the modulating influence of the combination of dual-mode brain stimulation over bihemi%ADspheric stimulation with motor training in TBI patients.

Twenty TBI patients with hemiparesis received five randomly arranged sessions of diverse combinations of tDCS and rTMS. We applied cathodal or anodal tDCS over the contralesional primary motor cortex (cM1) with 10Hz rTMS over the ipsilesional primary motor cortex (iM1) in a simultaneous or preconditioning method including sham stimulation. Immediately after dual mode stimulation, 5 minutes of sequential hand motor trainings were performed. The total pulses of rTMS and duration of tDCS and motor training was the same in all sessions. Cortical excitabilities and sequential motor performances were evaluated before and after each session.

Motor function and corticomotor excitabilities following simultaneous stimulation of cathodal tDCS with 10Hz rTMS were significantly increased after intervention with significantly greater motor improvements than other conditions ($P < 0.05$).

Conclusions. For the combination of bihemispheric tDCS and rTMS with motor training, simultaneous stimulation of cathodal tDCS over cM1 combined with 10Hz rTMS over iM1 followed by motor training results in better motor performance in TBI patients than other combinations of dual-mode stimulation. This may be due to mechanisms associated with interhemispheric interaction.

Key words
dual mode non invasive brain stimulation, motor training, rehabilitation, TBI, training induced plasticity

B1-04

MILD EXPERIMENTAL TBI INCREASES ETHANOL CONSUMPTION IN THE DELAYED POST-TBI PERIOD

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Alcohol intake patterns vary after traumatic brain injury (TBI), with initial decreases transitioning into delayed increases in consumption. To investigate this, our lab has focused on developing a model of mild TBI-induced changes in ethanol (EtOH) intake. Our previous studies demonstrated reduced binge-pattern drinking in the early post-TBI period. Here, we investigated the effects of mild TBI on chronic high-level EtOH consumption in the delayed post-TBI period using a chronic, intermittent access paradigm. C57BL/6 mice (6–8 wks old) received sham surgery or mild TBI over the midline suture of the intact skull. Beginning at 15 d post-injury, mice were evaluated for chronic high-level EtOH consumption using a chronic, intermittent EtOH access paradigm. Each 7-day cycle consisted of 24-h concurrent access to 20% EtOH (v/v in water) and water on days 1, 3, and 5, with access to water only on days 2, 4, 6 and 7. Mice were maintained on this consumption schedule for 44 days during which EtOH and water intake volumes were recorded daily. On the 45th day of consumption, mice were allowed only 2 h of EtOH/water access after which whole brains and blood samples were harvested. Brain-injured mice consumed significantly more EtOH than controls over the study duration. Interestingly, this result was driven by a delayed increase in consumption by TBI mice compared to shams that began only after 10

EtOH exposure sessions (day 24). During this delayed consumption period, injured mice demonstrated significantly increased intake compared to initial consumption volume on day 1 of EtOH access, which was not observed in controls. These data demonstrate that experimental mild TBI increases chronic EtOH consumption compared to controls and that this effect is pronounced in the delayed post-TBI period. These results reflect clinical observations of increased alcohol consumption in brain-injured patients in the prolonged recovery period, providing a useful tool for defining mechanisms underlying TBI-related alcohol dependence.

Key words
addiction, alcoholism, behavior, striatum

B1-05

VAGUS NERVE STIMULATION AND NONPARETIC LIMB TRAINING MODIFY STROKE RECOVERY

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Vagus nerve stimulation (VNS) is a safe, tolerable treatment that has been shown to drive powerful, long-lasting plasticity especially when paired with somatosensory inputs. VNS paired with rehabilitative training has been shown to improve functional recovery beyond what can be achieved by rehabilitative training alone in models of stroke. Though preclinical studies of stroke have repeatedly shown the beneficial effect of VNS on stroke recovery, clinical trials involving targeted plasticity therapy after stroke in humans have not been as successful. Stroke can cause impairments in the upper extremities. Early post-stroke rehabilitation by way of occupational therapy often includes extensive training of the unimpaired forelimb which can provide some immediate functional benefits, however recent studies suggest that this training may interfere with functional recovery of the paretic forelimb. To test this hypothesis, rats will be trained on a novel, skilled-reach force generation task to asymptotic performance. Upon attainment of task proficiency, a nonparetic forelimb training paradigm will be implemented following the induction of a chronic ischemic lesion, after which recovery of the paretic forelimb will be assessed. VNS will be paired with rehabilitative training and therapeutic potential in this model will also be assessed. After the completion of therapy, intracortical microstimulation techniques will be employed to develop high-resolution maps of the cortical representations of peripheral movements. We predict that the beneficial effects of VNS on stroke therapy will be blocked or reduced by early post-stroke training of the nonparetic forelimb. The effects of nonparetic forelimb training and VNS based therapies on stroke recovery will enrich the understanding of the neural mechanisms of functional recovery from stroke and could serve as evidence to challenge existing post-stroke clinical intervention strategies and improve stroke recovery in stroke patients.

Key words
stroke recovery, targeted plasticity therapy, vagus nerve stimulation

B1-06

EFFECTIVENESS OF THE SLICE CONCUSSION EDUCATION PROGRAM FOR CHICAGO YOUTH

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The Centers for Disease Control and Prevention states that between 1.6 and 3.8 million student athletes experience concussions each year. Sports Legacy Institute Community Educators (SLICE) is a student-run organization that teaches elementary, middle school, and high school students around the country about symptoms, associated risks, and appropriate responses to concussions. The original SLICE program in Boston was shown to have a significant impact on students' concussion knowledge (Bagley et al., 2012). DePaul University's SLICE program was the first chapter established outside of Boston, and therefore was assessed during its first year. In the present Chicago study, students in participating schools, ranging in age from 9–19 years ($N = 299$), were given an interactive presentation complete with demonstrations, discussions, and case studies. SLICE presenters gave participants surveys before ($n = 299$) and immediately after ($n = 272$) the program to assess knowledge of concussion symptoms and appropriate responses to a concussion. A one-tailed t-test showed a significant difference in mean survey scores between groups before and after the SLICE presentation ($t = -11.804$, $p < 0.0001$). A significant improvement in scores was observed such that scores increased by 17% after the presentation, from an average failing score (< 50%) to an average passing score (> 50%). Additionally, a binomial distributions test revealed that there was a significantly higher overall passing rate on the post surveys than on the pre surveys ($z = 6.86$, $p < 0.05$). Results also show that female students scored higher overall than males ($t = -5.902$, $p < .0001$). Preliminary results suggest that the SLICE program in Chicago is effective in promoting concussion knowledge. Further analysis will include the examination of surveys collected one-month post presentation to help determine sustainability of concussion knowledge.

Key words
concussion, education, mild traumatic brain injury

B1-07

NEUROENDOCRINE AND NUTRITION STATUS IN ACTIVE DUTY SERVICE MEMBERS WITH MTBI AND PSYCHOLOGICAL HEALTH DIAGNOSIS

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The objective is to characterize neuro-endocrine and nutritional status of service members (SM) returning from Iraq and Afghanistan with traumatic brain injury (TBI) and psychological health conditions being cared for in an interdisciplinary 4 week program at the National Intrepid Center of Excellence (NICoE). A fasting morning laboratory panel evaluating neuroendocrine (NE) function and nutritional status was obtained in the first week.

235 consecutive SMs comprised the sample (mean age 34.68 ± 8.2 years, 96.3% male, average time in service 12 ± 7.5 years, 82% with blast-related mTBI, and 85% with more than one mTBI. All SM were 6 months from time of last TBI. Laboratory results related to NE function and nutritional status were examined. BMI (average) = 28.29 ± 4.03.

Neuroendocrine Test Results (percentage of cohort with abnormal results): Insulin-like growth factor (IGF-1) 0.0%; Thyroid-stimulating hormone (TSH) 5.8%; Free T4 3.4%; Cortisol (serum) 18.86%; Free testosterone 8.84%; Follicle-stimulating hormone (FSH) 16.33%; Luteinizing hormone (LH) 4.00%, and Prolactin 13.23%. Nutritional Status Test Results (percentage of cohort with abnormal results):

Fasting glucose 10.13%; Folate (serum) 5.02%; RBC folate 8.74%; Vitamin B12 2.06%; Methylmalonic acid 0.44%; Vitamin D insufficiency (25-OH vitamin D < 30 ng/mL) 65.37%; Vitamin D deficiency (25-OH vitamin D < 10 ng/mL) 2.37%, and C-reactive protein (CRP) 6.12%.

Neuroendocrine dysfunction (NED) was identified in a minority of SMs. Compared to the estimated incidence (15% to 30%) of NED in patients with persistent symptoms following TBI without PH diagnoses, NED was less frequent in this study cohort. No abnormalities in IGF-1 were identified in this cohort, which is in contrast to the literature on growth hormone deficiency in patients with TBI. Secondary hypogonadism in this cohort will require further study regarding concurrent conditions, including obstructive sleep apnea, PTSD, and elevated prolactin levels. Nutritional abnormalities were frequent, especially Vitamin D. Nutritional abnormalities represent treatable sequellea of TBI.

Key words
chronic TBI, military, nutrition, trauma

B1-08

DOSE RESPONSE EFFECTS OF ACUTE ADMISTRITATION OF INTRATHECAL BACLOFEN (ITB) ON TBI-INDUCED SPASTICITY

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Spasticity is a major health problem for patients with moderate to severe traumatic brain injury (TBI) with a high incidence of inducing orthopedic disability. The use of anti-spastic medications, particularly ITB, can decrease the severity of spasticity produced by TBI. However, current federal guidelines preclude the use of ITB therapy during the first year following TBI due to insufficient data to assess risk of early therapies on cognitive, balance, and motor recovery. Therefore, an objective of the present study was to determine the safety, feasibility, and efficacy of early intervention treatments (initiated at one week and continued for 4 weeks) on the long-term outcome of spasticity, cognition, and balance recovery. Three doses were tested: low (0.4 μg/hr), medium (0.8 μg/hr), and high (1.6 μg/hr) of ITB (Lioresal®) treatments using Alzet osmotic mini-pumps in a TBI-induced spastic rodent laboratory model (Bose et al, 2012). Velocity dependent ankle torque & ankle extensor muscle EMGs (as measures of spasticity), rotorod balance performance, and the Morris water maze (MWM) for spatial learning were used to quantitate the dose-response effects of these early ITB treatment doses. Our data to date indicate that ITB treatment can significantly reduce spasticity in a dose-dependent manner. The medium dose (0.8 μg/hr) provided blockade of early onset spasticity, attenuated late onset spasticity, with minimal negative impact on balance and cognitive performances. These findings are consistent with minimum effective dose therapy that can provide a potent spasticity reduction while significantly decreasing the unintentional influence of medication on non-target CNS tissues that influence cognitive acuity or balance. Supported by Medtronic Inc. and VA Merit Review B6570R.

Key words
GABAb agonist, spasticity, therapeutic intervention, traumatic brain injury

B1-09

THERAPEUTIC TMS REDUCES TBI SPASTICITY, ANXIETY, AND PAIN

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TBI can initiate disabilities in cognitive performance, spasticity, anxiety, and pain that significantly impact the quality of life. Urgently needed are therapies that can provide safe and effective reduction in these long-term disabilities without negatively impacting cognitive recovery. We inadvertently observed potentially significant therapeutic benefits induced by an evaluation protocol that used TMS. The current studies were performed to systematically evaluate the potential therapeutic benefits induced by this TMS protocol following TBI in adult rats. Closed head (weight drop acceleration) TBIs were produced by a modification of the Marmarou procedure (450g x 1.25 m drop height). The TMS treatments consisted of single pulse TMS delivered to the surface of the cranium through a 25 mm figure 8 coil. An intensity ladder using 10% increments from 30% through 70% maximal intensity was delivered three times per week for one month. At the completion of treatment, cognitive performance was assessed using a serial learning paradigm in a Morris water maze (MWM). Spasticity was quantitated using velocity dependent ankle torque (VDAT) and triceps surae EMGs. Anxiety was assessed using an elevated plus maze. A test for thermal hypersensitivity was performed using a behavioral apparatus to quantitate facial contact to a thermode during drinking. Compared with intact animals, the TBI animals revealed significant increases in MWM escape latency, significant increases VDAT and TS EMGs, significant increases in time spent in closed arms of the plus maze, and significantly decreased facial contact with a thermode during drinking. Compared with the untreated TBI animals, the TMS treated TBI animals revealed a mean 83.1% reduction in spasticity, A 92% decrease in anxiety, and 95% decrease in thermal sensitivity. No changes in serial learning were detected between treated and untreated animals. These preliminary studies indicate a significant therapeutic reduction in three long-term TBI disability measures. (Supported by RR&D Merit B78071 & RR&D RCSA B7345S).

Key words
anxiety, pain, spasticity, TMS, traumatic brain injury

B1-10

COMBINING ENRICHED ENVIRONMENT, PROGESTERONE, AND EMBRYONIC NEURAL STEM CELL THERAPY IMPROVES RECOVERY FOLLOWING BRAIN INJURY

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Enriched environments (EE), progesterone (PROG), and embryonic neural stem cells (eNSC) have been investigated as treatments for traumatic brain injury (TBI). Post-injury EE increases cortical volume and increases the rate of eNSC survival. Progesterone has been shown to reduce cellular edema and apoptosis. Transplanted eNSCs reduce functional losses and have been shown to survive, migrate, and express neuronal characteristics. Since each approach hypothetically

addresses different secondary consequences; combining two or more of these therapies might have a cumulative effect. Therefore, the present study was designed to determine if any potential synergistic effects exist between the three approaches following TBI. Male Long-Evans rats received either a medial frontal cortex contusion injury or a sham surgery. After injury, animals were assigned to either an EE or standard environment (SE). Progesterone (10 mg/kg) or a vehicle was administered four hours post-surgery and every 12 hours after, for 72 hours. Half of the animals received ~100K eNSCs or media one week post-injury. Subjects were evaluated on the Barnes maze (BM), Morris water maze (MWM), and the rotorod (RR). Following the behavioral portion of the study, the animals were perfused, extracted, and prepared for histological investigation. The subjects that received all three therapeutic approaches performed significantly better than untreated injured subjects on all three behavioral tests. Stereological analysis revealed that animals that received eNSC and EE had greater cortical volume and the animals that received eNSC, PROG, and EE had a greater average number of cells in the hippocampus than any other treatment. Confocal immunofluorescence imaging combined with advanced optical clearing techniques (SeeDB) confirmed that eNSCs survived, migrated from the transplantation site, and expressed neural characteristics. These data suggest that a polytherapeutic approach improves recovery. However, the direct mechanism (independent or in combination) has yet to be elucidated. Future research should be focused on understanding how these approaches act together to improve recovery.

Key words
behavioral recovery, embryonic neural stem cells, enriched environment, polytherapy, progesterone, SeeDB

B1-11

IDENTIFICATION OF MILITARY OCCUPATIONS MOST LIKELY TO SUFFER MILD TRAUMATIC BRAIN INJURY (MTBI) AND RELATED SENSORY INJURIES

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Military return-to-duty decisions following mTBI are based on medical screening and physical readiness exams. Improving such decisions requires identifying occupations affected by mTBI and determining whether occupation-critical skills are disrupted.

This epidemiological study identified the occupations most susceptible to mTBI and related neurosensory problems. The team narrowed down 1,500 medical injury codes to the 25 most relevant to acceleration/blast injuries across four categories: head/brain, vision, auditory, vestibular. (These injuries will be presented since they are of interest to studies of neurotrauma and sensory disorders.) We identified the top-ten most-affected jobs in each of the 25 codes using data from the Defense Medical Epidemiology Database. The 250 most-affected jobs (with the highest rate of injured-versus-total personnel) were ranked by how frequently they occurred in the top-ten list for each injury category. These lists were used to identify the overall top-three most-affected occupations. Finally, we determined the critical skills needed to perform each job, to identify job-critical deficits.

The most relevant mTBI-related injury codes and categories were identified. We confirmed that some jobs are more likely to suffer from these injuries. The top-three most affected occupations were Infantry, Cavalry Scout, and Artillery. We determined that certain key injuries would disrupt job-critical performance of these jobs. Additionally, we found that Special Forces ranked in the top-ten for head/brain injuries but not any of the sensory injury categories, while Law Enforcement ranked in the top ten for sensory injuries but not head/brain.

mTBI and associated sensory disorders disproportionately affect certain military jobs in ways that make it difficult to perform those jobs. Certain key injuries disrupt abilities that are job-critical (e.g., firearms operation) and job-specific (e.g., Artillery gunnery); these injuries should be the focus of military neurotrauma research intended to improve rehabilitation and return-to-duty.

Key words
blast injury, fitness-for-duty, mild traumatic brain injury, military brain injury, return-to-duty

B1-12

PAIRING VAGUS NERVE STIMULATION WITH REHABILITATIVE TRAINING ENHANCES FUNCTIONAL RECOVERY AFTER TRAUMATIC BRAIN INJURY

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Traumatic Brain Injury (TBI) is one of the largest health problems in the United States, and affects nearly two million people every year. The effects of TBI, including weakness and loss of coordination, can be observed years after the initial injury. We have developed a method by which we drive cortical plasticity through stimulation of the vagus nerve during rehabilitative therapy to enhance recovery from TBI. We trained rats to perform the isometric pull task – a task that measures volitional pull strength. After animals were proficient at the task they received a controlled cortical impact in the forelimb area of left motor cortex, and were then randomized into two treatment groups. The first group of animals received vagus nerve stimulation (VNS) paired with rehabilitative therapy, while another group received rehabilitative therapy alone. We found that animals that received VNS paired with therapy achieved a full recovery of their forelimb strength, while animals that received only rehabilitative training did not significantly recover forelimb strength. Our findings indicate that pairing VNS with rehabilitative therapy enhances functional recovery, and further research is warranted to investigate how VNS may transfer to clinical settings.

Key words
vagus nerve stimulation

B1-13

B1-14

IMPAIRED NEUROGENESIS IN A RAT MODEL OF TRAUMATIC BRAIN INJURY

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Following traumatic brain injury (TBI), incomplete replacement of lost neurons by endogenous cells in the dentate gyrus (DG) of the hippocampus, summed to ongoing neurodegeneration, results in a range of cognitive dysfunctions that significantly affect the quality of life for post-traumatic brain injury survivors. The aim of this work was to study the process of neurogenesis in the rat hippocampus following moderate TBI.

We used adult male Sprague-Dawley rats and the fluid percussion injury model of TBI. Laser capture microdissected samples collected from the DG were analyzed using the ''Neurogensis RT^2 Profiler PCR array kit (Qiagen). Further analysis of the DG was performed by immunofluoresence using specific antibodies against neuronal progenitor cells and granule neurons.

Gene expression analysis showed that 2 weeks following moderate TBI, the expression of several genes known to play a role in neuronal differentiation, migration and survival was significantly reduced as compared to naïve rats. At the same time, we found a significant increase in the expression of both the ligand for the NOTCH receptor, DLL1, and the transcription factor STAT3, both known to be involved in promoting gliogenesis while suppressing neurogenesis. Further analysis of rat brain sections showed that the number of neuronal progenitor cells expressing DCX was significantly increased after TBI in both the ipsilateral and controlateral sites while the number of cells expressing both DCX and the mature neuronal marker NeuN was significantly reduced.

Our data show that although an increase of neural progenitor cells in the DG is observed after TBI, the maturation and integration of newly formed neurons is significantly reduced. Moreover, the increase in the expression of DLL1 and STAT3 in the SGZ strongly suggests that the suppression of neurogenesis is accompanied by a concurrent increase in gliogenesis. Underrstanding the mechanisms underlying impaired neurogenesis after TBI will aid the development of novel therapeutic interventions for the treatment of TBI survivors.

Key words
gene expression, hippocampus, neurogenesis, TBI

B1-15

ENVIRONMENTAL ENRICHMENT RESTORES COGNITIVE PERFORMANCE IN AN ATTENTIONAL SET-SHIFTING TEST AFTER TRAUMATIC BRAIN INJURY

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Cognitive impairment associated with prefrontal cortical dysfunction is a major component of disability in traumatic brain injury (TBI) survivors. Specifically, deficits in executive function and behavioral flexibility are present across all injury severities. While impairments in spatial learning have been extensively reported, experimental models of TBI investigating more complex cognitive disabilities are relatively scarce. 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. Previously, we demonstrated that a controlled cortical impact (CCI) injury (2.8 mm cortical deformation at 4 m/s) produced significant impairments in executive function and cognitive flexibility in the AST (Bondi et al., 2014, *J Neurotrauma*). The current study evaluated whether environmental enrichment (EE), a preclinical model of neurorehabilitation, would restore cognitive performance post-injury. Thirty-one isoflurane-anesthetized male rats received a CCI or sham injury and then were randomly assigned to TBI and sham groups that were further divided into EE and standard housing (n = 6-10/group). When tested at 4 weeks post-surgery, TBI impaired extradimensional set-shifting and stimulus reversal learning and increased total response errors and set loss errors (i.e., after 50% or more of the contingency rule has been achieved) ($p < 0.05$), which replicated previous findings from our laboratory. Moreover, EE exposure significantly attenuated the detrimental effects of TBI on cognitive performance in the AST, suggesting that EE may be a viable preclinical model of cognitive rehabilitation ($p < 0.05$). These novel findings demonstrate that executive function and behavioral flexibility deficits in our CCI model are sensitive to the beneficial effects of EE. Ongoing studies are evaluating pharmacological and cognitive rehabilitation therapies as a clinically relevant combinational paradigm, as well as elucidating mechanisms underlying the neuropsychological deficits.

Key words
attentional set-shifting, brain trauma, controlled cortical impact, environmental enrichment, functional recovery, pharmacotherapies

B1-16

LONGITUDINAL RECOVERY OF REACTION TIME IN ACUTE AND CHRONIC CONCUSSION PATIENTS

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Clinical reaction time (RT) is a valuable tool in a multifaceted sports concussion assessment battery. Eckner et al have shown that assessment of simple reaction time utilizing the RTclin drop-stick is a reliable clinical test with high specificity and sensitivity to the acute effects of concussion. Previous studies have demonstrated that RTclin is effective in distinguishing concussive effects when compared to baseline data. This study aimed to examine the use of RTclin in the early (≤ 30 days) and late (> 30 days) post-injury time periods in the absence of baseline values. Furthermore, we sought to determine whether recovery of function differed between groups.

A group of 53 concussed patients (30 early, 23 late) were evaluated at UCLA Sports-Concussion clinic. RTclin scores were recorded at the initial clinic visit and at one clinical follow-up for each patient. Mean RTclin scores were calculated as an average fall time prior to catch for eight trials with an 80 cm measuring stick.

Using Welch two sample t-test ($p = 0.05$) and a Yuen robust analysis ($p = 0.05$), reaction times of the entire group significantly improved between visits, from 243.91 ms (29.15 cm) to 230.53 ms (26.04 cm). Linear mixed effects modeling shows statistically significant effects due to clinic visit (initial vs follow-up), post-injury group (late vs early), days since injury, and their interactions. Further, multimodal inference places the highest emphasis on clinic visit, group, and group by visit interaction.

RTclin improvements were observed from initial visit to follow-up regardless of time since injury, and in both early and late patients. However, patients improved more if seen during the early post-injury period, and seen closer to date of injury. These results suggest RTclin

can be used to track both acute and chronic recovery following concussion. Future studies can investigate whether the improvements in RTclin were subject to practice effect, and what clinical interventions had the greatest effect on RTclin improvement.

Key words
concussion, mild traumatic brain injury, simple reaction time

B1-17

GENDER DIFFERENCES IN SYMPTOM REPORT FOLLOWING MILD TBI IN ADOLESCENTS AND YOUNG ADULTS DEPEND ON AGE

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Female gender has been associated with higher levels of post-mTBI symptoms and prolonged symptomatic recovery (Ponsford et al., 2012; Elbin, 2011). An examination of longitudinal symptom report in mTBI and orthopedic injury patients may elucidate the nature of these differences and inform the mechanisms underlying them.

Participants were adolescents and young adults aged 12–30 years. Sixty-six mTBI patients and 64 orthopedic injury controls were recruited as a consecutive series of admissions to emergency centers of three Level-1 trauma centers. Patients were administered the Rivermead Post-Concussion Symptom Questionnaire at 96 hours and 3 months post-injury. Generalized Estimating Equations were used to assess age-related group and gender differences in symptoms over time.

Results revealed a significant group effect on total symptom score ($X^2_1 = 39.7$, $p < 0.0001$) with mTBI patients reporting more symptoms than orthopedic injury patients. Symptoms decreased over time for both groups ($X^2_1 = 13.9$, $p = 0.0002$), and females in both groups reported more symptoms than males ($X^2_1 = 7.6$, $p = 0.0059$) However both of these effects were dependent on age (time*age: $X^2_1 = 4.3$, $p = 0.0042$; gender*age: $X^2_1 = 4.3$, $p = 0.0393$), such that older patients demonstrated poorer symptomatic recovery than younger patients, and gender differences in symptom report dissipated with age.

The girls and young women in our sample reported greater symptom severity following both mTBI and orthopedic injury. However, this gender difference was only evident among younger participants. Like the older females in our sample, older males reported a higher level of symptoms at 96 hours post-injury, relative to younger males, and their symptoms remained stable at 3 months post-injury. Possible mechanisms underlying these effects will be discussed.

Key words
concussion, mTBI, sex differences, symptoms

B1-18

VERIFICATION OF CIRCUIT-DIRECTED REHABILITATION PARADIGM FOR BRAIN INJURY-INDUCED CIRCUIT REORGANIZATION

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After experimental diffuse traumatic brain injury (TBI), there is behavioral, functional, molecular and neuropathological evidence that injured circuits are immediately disrupted, then dismantled and eventually reorganized. In rodents, by 28 days post-TBI, late-onset sensory sensitivity to whisker stimulation is a phenotypic expression of maladaptive circuit reorganization in the somatosensory thalamocortical circuit. A molecular biomarker of circuit activation and integrity could determine the impact of type, onset and duration of therapeutic intervention on circuit reorganization. Activity-regulated cytoskeleton-associated protein (Arc), an immediate early gene, has gene expression tightly coupled to behavioral paradigms *in vivo,* including injury-induced changes with manual whisker stimulation. In these experiments, we determine the dynamics of Arc transcription after whisker somatosensation in a natural environment as a potential approach for therapeutic intervention. For this study, adult male Sprague Dawley rats (~300g) were encouraged to explore novel tubes for 15 minutes to activate the whisker circuit. At various time points following whisker stimulation, tissue biopsies were removed from primary somatosensory barrel field (S1BF) cortex and ventral posterior medial nucleus (VPM) of the thalamus for quantitative real-time PCR analysis for comparison with exploration-naïve rats. Whisker stimulation through novel tubes resulted in a 8-fold increase Arc mRNA expression at 30 minutes in the S1BF in comparison to naive ($F(4,13) = 4.417$; $p = 0.018$). There were no changes in Arc expression in the VPM. These data demonstrate that exploration through novel tube configurations is capable of directed activation of the whisker circuit. Exploration of tube configurations may be useful as a verification of circuit-directed rehabilitation for brain injury-induced circuit reorganization.

Supported, in part, by NIH R03 NS077098, NIH R01 NS065052 and PCH Mission Support

Key words
circuit reorganization

B1-19

INCIDENCE OF OUTPATIENT FOLLOW-UP SERVICES IN FUNCTIONALLY-RECOVERED MILD TBI PATIENTS

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To date, uniform standards for follow-up of mild traumatic brain injury (mTBI) patients remains elusive. Although there exists a myriad of multidisciplinary services for TBI outpatient rehabilitation, access is problematic due to underdiagnosis, lack of coverage, and inadequate systems for coordinating outpatient care. Typically resources are utilized by moderate to severe TBI patients and less available to the mTBI population. Statistics regarding the percentage of mTBI patients returning for follow-up also have not been systematically compiled. The Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) Pilot Study collected NIH Common Data Elements (CDEs) regarding the type and frequency of follow-up services after discharge from acute care. These self-reported finding were analyzed with a cohort of TBI patients presenting at three Level 1 Trauma Centers who underwent brain CT. To target mTBI in the functionally recovered as the main effect, patients with admission GCS < 14, extracranial abbreviated injury scale score of > 2, unfavorable outcome by Glasgow Outcome Scale Extended (GOSE) of 1-4 at 6-months or received inpatient rehabilitation during recovery

were excluded from this analysis. In 248 patients, 41% had GOSE 8 (Upper Good Recovery), 31% had GOSE 7 (Lower Good Recovery), and 28% had GOSE 5-6 (Moderate Disability). Twenty-nine percent received outpatient care (18% of GOSE 8, 32% of GOSE 7, and 40% of GOSE 5-6). These results show that the majority of mobile patients without full recovery (GOSE 5-7) on their global outcome have not had any form of outpatient follow-up. Detailed reasons for this lack of follow-up is not well understood, and more granular information regarding outpatient services should be collected to better triage and allocate resources to this population.

Key words
human studies, outcome measures, outpatient care, traumatic brain injury

B1-20

ATTENTION, MEMORY AND EXECUTIVE FUNCTION DEFICITS IN PATIENTS WITH COMPLICATED VS UNCOMPLICATED MILD TRAUMATIC BRAIN INJURY

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Neuropsychological deficits are a common but under-reported sequel of traumatic brain injury. This phenomenon is more pronounced among patients with mild traumatic brain injury (mTBI) who are not formally assessed, thereby missing an opportunity for early neuropsychological intervention.

We sought to examine the early neuropsychological deficits observed in patients with complicated mTBI (presence of intracranial lesions on radiological imaging) and uncomplicated mTBI (no intracranial lesions on radiological imaging).

We prospectively recruited 60 patients with mTBI (Glasgow Coma scores of 13 to 15) due to road traffic accidents presenting to the Emergency Department of a Level 1 Trauma Centre. The patients were selected based on the preset inclusion and exclusion criteria. Neuropsychological evaluation was performed using the Screening Module of Neuropsychological Assessment Battery (S-NAB) within the same admission.

The mean score differences of neuropsychological performance between the complicated versus uncomplicated groups were calculated. The differences were adjusted for age, gender, level of education, injury severity (GCS) and outcome (GOSE) at discharge. There were significant differences between the groups (complicated vs uncomplicated) in terms of their age range and also gender distribution.Independent samples t-tests found significantly lower S-NAB Index overall scores in patients with complicated mTBI compared with uncomplicated mTBI. These patients had a higher preponderance of attention, executive function and memory related impairments.

Classifying mild traumatic brain injury as complicated or uncomplicated may help further identify patients who are likely to develop significant neuropsychological sequelae. A larger cohort of patients and a longer period of review is needed to verify these findings.

Key words
attention, brain imaging, complicated vs uncomplicated, executive function, mild traumatic brain injury, neuropsychological outcome

B1-21

ATTENUATED ELECTROPHYSIOLOGICAL RESPONSE TO FEEDBACK FOLLOWING SPORTS CONCUSSIONS

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Among a growing number of studies suggesting that concussions affect cognition in the long term, a recent study showed that the electrophysiological response to errors in both visuospatial attention and working memory task was significantly altered in multiply concussed athletes.

The aim of the present study was to investigate the long term and cumulative effects of concussions on the neurophysiological correlates of feedback processing in asymptomatic concussed athletes.

For this purpose, the *Feedback-related negativity* (FRN) component was recorded during a visual short-term memory task in which a feedback on the performance was provided after each trial. Thirteen concussed athletes (number of concussion ranging from 1 to 5) and 13 athletes with no history of concussion participated in the study.

Athletes with a history of concussion showed a significant FRN amplitude reduction compared to control athletes ($F_{1,25} = 4.34$, $p < .05, = .1532$). Moreover, a subsequent correlational analysis suggested that the number of concussions sustained was predictive of the amplitude of the FRN ($r = 0.40$; $p < 0.05$), such that those athletes whose FRN amplitude was more suppressed were those who had sustained more concussions. These findings suggest that the neurophysiological response to performance feedback is significantly affected following concussions and that this alteration increases with the number of concussions sustained.

Key words
cognitive control, event-related potentials (ERPs), feedback-related negativity, sports concussion

B1-22

FEDERAL COORDINATION FOR TRAUMATIC BRAIN INJURY RESEARCH: THE NATIONAL RESEARCH ACTION PLAN

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On August 31, 2012, President Obama promulgated an Executive Order (EO) directing the Departments of Defense (DoD), Veterans Affairs (VA), Health and Human Services (HHS), and Education, with additional coordination with the Centers for Disease Control, to develop and execute a National Research Action Plan (NRAP) on posttraumatic stress disorder (PTSD), other mental health conditions, and Traumatic Brain Injury (TBI) ''to improve the coordination of agency research into these conditions and reduce the number of affected men and women through better prevention, diagnosis, and treatment.'' [1,2] The NRAP outlines short, mid and long-term research

and research management priorities as well as how the agencies will begin to address them. Issues to be addressed regarding TBI include development of a more precise classification system of TBI, identification of objective end points to improve the sensitivity of therapeutic trials, identification and organization of tissue repositories, improving patient reintegration into society, enhancing sharing of research data and investigation of means by which electronic medical records can be utilized for epidemiologic and clinical studies. This effort has stimulated closer coordination within and between the federal neurotrauma and mental health fields which adds value to the efforts given the frequencies of traumatic and psychological comorbidities. The National Neurotrauma Symposium offers an excellent opportunity to share our progress and to seek feedback from the research community.

1. Improving Access to Mental Health Services for Veterans, Service Members, and Military Families. Executive Order. The White House.
2. National Research Action Plan.

Key words
federal funding agencies, research coordination, strategic planning

B2-01

MESOPOROUS SILICA NANOPARTICLES CAN DELIVER PTEN INHIBITOR AND ENHANCE NEURONAL REGENERATION EFFECTIVELY

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Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is known to regulate the axonal regrowth of central and peripheral nervous systems, and PTEN inhibition can facilitate axonal outgrowth following nerve injury. However single application of PTEN inhibitor to the injured neurons is not sufficient for long-term regeneration of outgrowing axons. Mesoporous silica nanoparticle (MSN) has a large surface area, high pore volume and intrinsic biocompatibility which enable absorption and release of multiple drugs and biomolecules. Therefore we planned to use MSN as a drug delivery system for PTEN inhibitor, bisperoxovanadium (BpV) (HOpic) through in vitro and in vivo studies for the first time. We prepared dorsal root ganglion (DRG) from adult Sprague-Dawley (SD) rats for in vitro study, and the cervical roots in SD rats were crushed with forcep for 5 seconds for in vivo study. Various concentration of BpV, MSN and BpV-conjugated MSN was tested to detect optimal condition for cell viability and axonal regeneration for 5 days. We found that the application of 20ng BpV conjugated with 20 μg/ml MSN to primary cultured DRG showed the best cell viability and maximal axonal outgrowth. With the same concentration, we injected BpV-conjugated MSN (1 μg/per DRG) into the damaged DRG in rats and found that outgrowing axons crossing injury site were increased and faster than vehicle controls. We conclude that mesoporous silica nanoparticles can deliver PTEN inhibitor to neurons effectively and enhance neuronal regeneration in vitro and in vivo conditions.

Key words
mesoporous nanoparticle, PTEN inhibition

B2-02

DIRECTLY REPROGRAMMED NEURAL STEM CELLS ENHANCE FUNCTIONAL RECOVERY FOLLOWING SPINAL CORD INJURY IN RATS

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Injured spinal cord is hard to be regenerated, and there is as yet no proven fundamental treatment in the clinical setting. Regenerative strategies using stem cells and biomaterials have revealed some functional improvements following spinal cord injury (SCI) in the experimental field, however there are many hurdles to be applied in the clinical field. Direct reprogramming of somatic cells into neural stem cells has many advantages including reduced tumorigenicity, no need to perform additional in vitro differentiation before transplantation, and multipotency only to differentiate into neural and glial cells with capable of autologous transplantation. Recently, we reported that mouse embryonic fibroblasts (MEFs) were directly converted into the induced neural stem cells (iNSCs) using four transcription factors (*Brn4*, *Sox2*, *Klf4*, and *c-Myc*) without the production of induced pluripotent stem. We transplanted iNSCs into contused spinal cord in Sprague-Dawley rats and found that locomotor functions including Basso, Beattie, and Bresnahan (BBB) score and ladder score were improved following iNSC transplantation more than those in vehicle controls. Transplanted iNSCs were migrated and differentiated well into neurons, astrocytes, and oligodendrocytes, and formed synapse to host neurons within grafted site 12 weeks following transplantation. The inflammatory cells including macrophages and monocytes were reduced within the cavity in the injured site and the cavity size was also reduced 12 weeks following transplantation. This study is the first trial to investigate the effect and the therapeutic potential of directly converted iNSCs from mouse fibroblasts in the rat SCI model.

Key words
directly reprogrammed neural stem cell, in vivo differentiation, spinal cord injury, transplantation

B2-03

USING TRANSCRIPTION FACTORS TO PROMOTE THE SURVIVAL OF TRANSPLANTED CELLS FOR SPINAL CORD INJURY REPAIR

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Cellular transplants offer a multifaceted approach for spinal cord injury (SCI) repair. Despite significant progress in understanding their therapeutic potential, a common feature of all cell transplants, which may have detrimental affects on the use of transplants clinically, is the

early death of transplanted cells. The precise cause of transplanted cell death remains elusive and strategies that significantly enhance transplant survival have not yet been developed. To date, strategies to prevent transplanted cell death have focused on either blocking induction of cell death or blocking cell death signaling once started. Although there has been some success with these strategies, the presence of multiple cell death inducers and complex cross-talk between cell death pathways once activated have meant that the effects of the aforementioned strategies are modest. An alternative strategy is to counteract acute cell death signaling via direct activation of prosurvival pathways. One method to elevate prosurvival pathways in cells is to activate transcription factors involved in endogenous adaptive responses to stress. Among the transcription factors implicated in adaptive cellular responses to stress are the hypoxia inducible factors (HIFs). In the current study we examine the effect of enhancing HIF activity in Schwann cells transplanted into the injured spinal cord of rats. We demonstrate that transplanted cells normally have low levels of HIF transcriptional activity and that enhancing HIF activity through either overexpression or pharmacological manipulation results in improved survival of transplanted cells. This suggests that transcription factor activation may be a beneficial strategy for promoting the survival of transplanted cells.

Key words
cell survival, hypoxia inducible factor, Schwann cells, spinal cord injury, transcription factor, transplantation

B2-04

B2-05

DEVELOPMENT OF A LUMBAR SPINAL CORD INJURY MODEL TO EXAMINE THE THERAPEUTIC POTENTIAL OF TRANSPLANTING NEURONALLY INDUCED NSPCS

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Patients with injuries to the thoracolumbar region of the spinal cord often lose clusters of neurons that are essential for locomotion. Our focus is on replacing lost neuronal circuitry by transplanting adult spinal-derived neural stem/progenitor cells (NSPCs) that have been differentiated into neurons in vitro. We hypothesize that optimal differentiation of NSPCs in vitro towards a neuronal lineage will promote transplant survival and functional recovery after transplantation in the injured lumbar spinal cord.

NSPCs were treated with 1mM dibutyryl-cyclic AMP (dbcAMP) to enhance neuronal differentiation and stained with BIII tubulin to confirm neuronal character. To characterize the lumbar spinal cord injury model, various modified aneurysm clips (56 g, 35 g, 26 g and 20 g) were applied to 40 adult female Wistar rats (Wi) to assess spontaneous functional recovery as measured by the open field BBB locomotor scale. 40 (Wi) rats were injured with a 26 g clip and split into 4 treatment groups: (1) dbcAMP treated cells + Rolipram injection (RI) post-op, (2) dbcAMP treated cells + saline injection (SI), (3) untreated cells + RI, (4) media injection control + SI. Four hundred thousand cells were transplanted 1mm rostral and caudal to the injury site in the subacute phase of injury.

DbcAMP robustly differentiated NSPCs towards BIII positive neurons: $72\% \pm 6.3$. Rats recovered spontaneously to 2 ± 1 in the most severe 56 g group, 2.5 ± 1 in the 35 g group, 4 ± 2.5 in the 26 g group and 8.5 ± 2.5 in the 20 g group after 6 wks. In the transplant study, rats in the double treatment group (dbcAMP cells + RI) improved to a statistically significant ($p < 0.05$) average of $5.16(\pm 3.2)$ compared to dbcAMP + saline $= 2.2(\pm 1.5)$, untreated cells + RI $= 1.1(\pm 1.07)$ or control $= 2.2(\pm 1.3)$.

We have generated a novel pre-clinical lumbar spinal cord injury model and displayed that transplant of neuronally differentiated stem cells results in increased functional recovery.

Key words
CPG, cyclic AMP, lumbar, neural stem cell, neuronal differentiation, spinal cord

B2-06

DOMAINS OF NEURAL CONTROL OF WALKING IN HUMAN SPINAL CORD INJURY

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Measures of walking function based on time-distance parameters, although clinically meaningful for determining ambulatory capacity, provide limited information on gait quality and changes in neural control after injury. In incomplete spinal cord injury (iSCI) disentangling different domains of neural control of walking and a stratification of

patients based on their specific impairment may contribute to more targeted treatment strategies.

A comprehensive analysis of gait-related data, including time-distance and kinematic parameters as well as measures of lower-limb strength was performed over a range of walking speeds in 22 iSCI patients and 21 healthy controls.

iSCI patients remained capable to modulate step length, cadence, and gait-cycle timing (interlimb coordination) within their speed range despite severe limitations in walking velocity (~50% reduction). However, hip-knee coordination (intralimb coordination) remained distinctly altered and was inappropriately modulated at increased walking speeds. This measure and its quantifiable characteristics may reveal the severity of functional impairment and allow for patient stratification. Principal component analysis (PCA) applied on the multivariate set of gait data revealed that the largest variance was determined by parameters of walking speed and movement dynamics (PC1 45%), while measures representing interlimb (20%) or intralimb (12%) coordination came to lie along the PC2 and PC3 axes, respectively.

In iSCI distinct clusters of interrelated gait parameters can be discerned that may reflect distinct domains of neural control of walking. Data-driven analysis of gait-related parameters may improve the evaluation of therapeutic interventions and accelerate the identification of targeted interventions to increase locomotor outcome in iSCI.

Key words
gait pattern, locomotion, motor control, spinal cord injury

B2-07

HINDLIMB MUSCLE STRETCH REDUCES LOCOMOTOR FUNCTION AFTER A SPINAL CORD INJURY: ACUTE AND CHRONIC TIME POINTS

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After spinal cord injury (SCI), patients commonly develop spasticity and contractures as secondary complications of ''upper motor neuron'' lesions. Physical therapists use stretching maneuvers to maintain extensibility of soft tissues and to manage spasticity. However, available evidence that supports stretching as an effective rehabilitation technique is unconvincing. Previous studies in our lab found that stretching has negative effects on locomotor recovery in rats with acute mild thoracic SCIs. The present study utilized a more clinically relevant moderately-severe contusion injury, to determine the effects of stretching on locomotion at acute and chronic time points and to observe how stretching influences in-cage activity. Female SD rats with 25 g-cm T10 contusion injuries received our standard 24-minute stretch protocol, daily for 5 weeks starting 4 days (acute) or, for 4 weeks starting 12 weeks (chronic) post-injury. Deficits in locomotion were evident in the acute animals after only 5 days of stretching. As animals regained muscle tone by week 3 post-injury, 'therapists' had to apply more pressure during stretch in order to achieve a normal end range of motion. A more intense stretch, which was maintained for the following 2 weeks, resulted in even greater impairments in locomotion. In the chronic group dramatic drops in locomotor function were also observed after only 5 days, and most animals had BBB scores of 0–3 for weeks 2, 3 and 4 of stretching. Importantly, overnight activity did not differ between acute and control groups at any time point. However, the chronic group traveled significantly less distance during the weeks of therapy, presumably due to their severe hindlimb deficits. Locomotor function recovered to the control levels for both stretch groups within 3 weeks once daily stretching ceased. Our findings show that stretching has an acute and temporarily detrimental effect on locomotor recovery for animals with moderately-severe contusion SCI.

Key words
locomotion, stretching

B2-08

IMPROVING LOCOMOTION IN SPINAL CORD INJURED RATS: A BIOENGINEERING APPROACH

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Spinal cord injury (SCI) represents a significant health world problem. Multidisciplinary approaches such those presented by tissue engineering (TE) concepts hold great promise for SCI treatment. Therefore the objective of the present work focused on the development of a TE approach based on biodegradable polymers, 3D printing techniques, adipose stem cells and olfactory ensheathing cells, aimed at inducing the regeneration within SCI sites. 3D rigid tubular structures with different thickness layers as well as different pore geometry and orientation were processed using 3D plotting, a rapid prototyping technology. Additionally, click chemistry techniques were used to immobilize the GRGDS peptide into the gellan gum hydrogel. Then, both the tubular scaffolds and de hydrogel were combined in order to obtain a hybrid structure. Biological evaluation of the structures was firstly carried out by determining their cytotoxicity, followed by the encapsulation of stem cells on the gel phase. Results of the cytotoxicity assays revealed that the scaffolds were non cytotoxic. Moreover, chemical modification on the gellan gum hydrogel had a profound influence on cell growth and morphology. Afterwards, scaffolds were implanted on a rat hemisection model of SCI. Locomotory evaluation was performed using BBB, open field and rotarod tests. The *in vivo* evaluation revealed a good integration and an absence of inflammatory response to the scaffolds implantation. Moreover animals implanted with the biodegradable structures showed significant improvements on BBB motor scale and on the activity box. In addition, the combinatorial treatment led to a reduction in astroglyosis and inflammatory response. In conclusion, our TE approach holds great promise for SCI repair. Future work will be focus on the use of our TE treatment in a contusion SCI model.

Key words
adipose stem cells, biomaterials, olfactory ensheathing cells, spinal cord injury regeneration, tissue engineering

B2-09

UMBILICAL CORD MATRIX CELL SECRETOME REDUCES VASCULAR PERMEABILITY & LESION VOLUME AFTER TRAUMATIC SPINAL CORD INJURY

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Spinal cord injury (SCI)-induced vascular disruption (VD) is a trigger for secondary injury. Thus, targeting VD may reduce tissue loss and impairment. Mesenchymal Stem Cells (MSCs), including those from the human umbilical cord matrix (HUCMCs), have pericytic attributes. They are well suited to addressing VD and the multi-factorial dynamic SCI pathophysiology. However, SCI treatment with live cells is severely hampered by logistical and practical considerations.

A novel, viable, safe and effective alternative to acute cell therapy for SCI.

R&D ELISA arrays were employed to profile serum-free media conditioned by age- and passage-matched cells cultured for 2 weeks in DMEM/F12 + 1% Glutamax. Concentrated HUCMC secretome (>9kDa) was systemically infused immediately after traumatic 1-minute C7 clip-compression SCI in 250–300g female Wistar rats, which were sacrificed 48 hours later. Vascular permeability was evaluated by spectrophotometric quantification of 2% Evans Blue dye infused 30 minutes pre-sacrifice in snap-frozen homogenates of lesional spinal cord tissue. Pre-sacrifice very-high-resolution ultrasound (VHRUS) measurements of haemorrhagic lesional volume were made.

HUCMCs secrete more and greater concentrations of pro-angiogenic factors (activin, angiogenin, angiopoietin-1, amphiregulin and coagulation factor III), anti-inflammatory cytokines (G-CSF, GM-CSF, IL-6, IL-8, ENA-78, MCP-3, midkine, MIP-1alpha/beta and MIP-3alpha) and neurotrophic factors (FGF2, FGF7 and GDNF) than adult bone marrow stromal cells (BMSCs) and (adult and newborn dermal) fibroblasts. At 48 hours post-SCI, lesion-induced vascular permeability ($p = 0.0067$, $n = 5$) and lesion volume size ($p = 0.001$, $n = 4$) were both reduced by concentrated HUCMC-CM relative to controls (concentrated Alpha-MEM). Inflammation (measured by MPO activity) and haemorrhage (measured using Drabkin's reagent) were only slightly reduced intra- and peri-lesionally.

HUCMCs have a more potent secretome than BMSCs and fibroblasts, and can reduce SCI-induced VD.

Key words
cervical, conditioned medium, Drabkin's, Evans blue, mesenchymal, secretome, spinal cord injury, ultrasound, umbilical cord matrix, vascular permeability

B2-10

FUNCTIONAL IMPROVEMENT WITH INTRANASALLY-DELIVERED HUMAN OLFACTORY STEM CELLS AND EXERCISE AND ENRICHMENT IN SPINAL CORD INJURY

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We hypothesized that exercise and environmental enrichment may produce greater functional improvement when combined with intranasally-delivered progenitor cells after spinal cord injury. Thirty male, athymic Nude rats (3 groups, 10 rats each) were injured at T9 spinal level using the MASCIS device. Two weeks later, Group 1 received intranasal saline, Groups 2 & 3 received intranasally-delivered human olfactory-derived progenitor cells and Group 3 additionally received enrichment and exercise. Exercise consisted of passive cycling, low- and high-level swimming, perturbation training and voluntary exercise in exercise balls. Environmental enrichment involved exposure to a social environment with novel objects. Outcome measures included the BBB, the Louisville Swim, Inclined Plane and Beam tests. A statistical difference ($p = 0.027$) using repeated measures ANOVA was obtained with the Beam test where the progenitor, exercise/enrichment group improved more than the progenitor cells alone group. Poor health in the Nude rats may be responsible for lack of even greater functional improvement. Immunohistochemistry using anti-human antibody revealed that the intranasally-delivered progenitor cells homed to the region of damage in the spinal cord. The greater functional improvement in rats receiving the olfactory progenitor cells, exercise and enrichment may suggest that progenitor cells require input in order to form appropriate circuitry necessary for functional improvement. This therapeutic approach has great potential for clinical translation because a person's own olfactory progenitor cells with a normal neural fate could be used. The cells are obtainable and deliverable with minimally invasive techniques. The recently discovered method of intranasal delivery (no injections) would mean that even patients with severe spinal injuries may be able to be treated subacutely.

Key words
enriched environment, exercise, intranasal delivery, progenitor cell

B3-01

ACUTE STRESS COMPLICATING MILD TRAUMATIC BRAIN INJURY IN RODENTS

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Mild traumatic brain injury (mTBI) in humans often occurs in the setting of acute stress (AS), especially with military injuries. It is not clear if AS significantly contributes to the chronic symptoms that occur after mTBI. Rodent models of mTBI do not share this characteristic because the animals are anesthetized at the time of injury. The purpose of this research was to study the effect of AS either immediately before or after a mild cortical impact injury (mCCI) on behavioral consequences of the injury.

Forty Long Evans rats, weighing 300–350 grams, were enrolled and randomly assigned to five groups: sham ($n = 8$), AS ($n = 8$), mCCI ($n = 8$), AS induced 1 hr after mCCI ($n = 8$), and mCCI induced 1 hr after AS ($n = 8$). To induce AS, rats were placed in a 1′ by 1′ enclosure with a cotton ball scented with trimethylthiazoline and subjected to white noise at random intervals for 15 minutes. Rats undergoing mCCI were anesthetized and subjected to a mCCI [3 m/sec, 2.5 mm deformation]. Outcome measures were beam walking and balance tests, novel object recognition test, open field test, and two Morris water maze variations for spatial navigation and working memory.

The mCCI animals had impaired performance on beam balance testing compared to sham ($p = .029$), and a trend for impaired working memory on the Morris water maze testing ($p = .086$). The AS animals had significant differences on the open field test, with greater distance traveled ($p < .001$) and greater velocity of movement ($p < .001$) compared to sham, but no impairments on the motor or cognitive tasks. When mCCI was complicated by AS, there was no greater impairment on the behavioral tasks than with mCCI alone. These animals with the combined injury did not have the increased activity on the open field testing as those with AS alone.

AS induced by exposure to predator scent did not worsen performance on the behavioral tasks following mCCI, but the mCCI seemed to blunt the abnormalities on the open field activity testing seen with AS alone.

Key words
acute stress, fear response, impact injury, TMT, traumatic brain injury, trimethylthiazoline

B3-02

EFFECT OF AGING ON COGNITIVE OUTCOME AND NEUROINFLAMMATORY RESPONSE AFTER TRAUMATIC BRAIN INJURY

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Traumatic Brain Injury (TBI) can alter neuronal function and inflammatory responses even beyond the site of injury. TBI outcomes are worse in elderly patients including higher fatality rates and greater severity of TBI-related disabilities. In animal models recapitulating TBI, aging predisposes exacerbated neuronal loss, inflammation, and motor function acutely. However, no mechanism for age-related exacerbation of TBI has been identified. In the current study we investigated the effect of aging on TBI-induced cognitive deficits and neuroinflammatory response. TBI was induced by controlled cortical impact over the right parietal cortex in 3 and 18 month old male mice. Thirty days after injury, hippocampal-dependent learning and memory functions were measured using the radial arm water maze (RAWM) which consists of eight arms with an escape platform located at the end of one arm. Our data demonstrates that both age and TBI increases the number of errors that the animal commits to locate the escape platform when compared to their respective young and sham controls.

Many studies have shown that reducing the pro-inflammatory response can alleviate TBI-induced outcomes. While acute pro- and anti-inflammatory responses are exacerbated by age, it is unclear if the pro-inflammatory response is prolonged or if the anti-inflammatory response is diminished over time in old animals as compared to young animals. We characterized the inflammatory response of the injured brain in young and old animals by quantitative PCR on isolated microglia/macrophages from the injured hemisphere at a sub-acute time point 7 days after injury. Our results demonstrate that 7 days after injury there was a significant decrease in anti-inflammatory cytokine and M2 macrophage expression in old animals compared to the young. These data suggest an imbalance in the regulation of inflammation in the aging brain which may sustain a proinflammatory environment after injury.

Key words
aging, cognition, mice, neuroinflammation

B3-03

FRONTAL LOBE INJURY AND PREFRONTAL CORTEX-DEPENDENT FUNCTIONS IN MICE

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Traumatic brain injury (TBI) is the leading cause of neurological disability in the world. The majority of studies with open-skull TBI mouse models have utilized injuries over the parietal cortex and characterized hippocampal dependent functions and motor recovery. However, TBI often results in damage in the frontal lobe and induces chronic cognitive, emotional, and social behavioral sequelae that affect the long-term outcome and quality of life of human patients. Prefrontal cortex (PFC) functionality can be impaired after TBI as illustrated through poor performance on the Wisconsin Card Sorting Test (WCST) which assesses attentional and affective set shifting behavior. Mice likewise can develop affective and attentional sets and their ability to perform affective and attentional set shifting is disrupted by neurotoxic lesioning of the orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC) respectively. The set shifting paradigm (SSP) can be employed in an analogous manner to the WCST to determine region-specific functionality of the PFC in mice.

TBI was reproduced using controlled cortical impact in three month-old male *C57BL6/J* mice to the right frontal lobe. Thirty days after surgery, animals were tested on the SSP and the elevated plus maze (EPM) to characterize PFC-mediated attentional and affective set shifting and anxiety. The SSP demonstrated that mice with a frontal TBI committed more errors during affective set shifting but were comparable to sham control animals on attentional set shifting implying an impairment of OFC function without alteration of mPFC function. The EPM revealed a trend for TBI animals to spend less time in the open arm of the maze which suggests greater anxiety in animals with a frontal lobe TBI though the data was not significant. Neuron, astrocyte, and microglia/macrophage numbers were then examined after behavioral testing to characterize the injury.

Key words
animal model, cognition, prefrontal cortex, traumatic brain injury

B3-04

PRIMARY BLAST INJURY ELIMINATES LONG-TERM POTENTIATION IN RAT ORGANOTYPIC HIPPOCAMPAL SLICE CULTURES

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Blast-induced traumatic brain injury (TBI) is of growing concern for military personnel. This study investigated the effect 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 4–6 days following injury using 60-channel microelectrode arrays. Three functional measures (stimulus-response [S/R], paired-pulse [PP], long-term potentiation [LTP]) were recorded following either a sham, mild (336 kPa/0.84 ms/87 kPa·ms) or moderate injury (424 kPa/2.31 ms/248 kPa·ms). Stimulating with increasing current and fitting the voltage response to a sigmoid function generated S/R data. PP ratios were produced by injecting two successive electrical stimuli with increasing interstimulus intervals (ISIs) and dividing the amplitude of the second response by the first at each ISI. LTP was induced in CA1,

via the Schaffer collateral (SC) pathway, using 100Hz tetanic constant-current stimuli. Potentiation was calculated as the change in average response over the last 10 minutes of post-LTP recordings divided by the average response over the last 10 minutes of pre-LTP recordings.

After blast injury, in response to mossy fiber (MF) pathway stimulation, S/R activity was slightly decreased in CA1 and CA3 regions. No changes were seen with SC stimulation. After moderate blast injury, PP ratios at shorter ISIs were marginally increased. However, long-term potentiation was completely disrupted after both mild (-8±3%) and moderate blast (8±5%), when compared to sham exposure (53±9%).

In previous studies, mild blast exposure did not cause cell death [Effgen GB, *J.Neurotrauma*, 2014]. We conclude that primary blast injury eliminates LTP, even without cell death, while leaving other measures of evoked activity largely unchanged. LTP deficits may explain memory loss commonly observed in TBI patients. Future research will elucidate the mechanisms responsible for the disruption of LTP following primary blast injury.

Key words
blast, in vitro, TBI

B3-05

ELECTROPHYSIOLOGICAL EVIDENCE OF AUDITORY AND COGNITIVE DYSFUNCTION IN VETERANS EXPOSED TO HIGH-INTENSITY BLASTS

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During the recent conflicts in Afghanistan and Iraq (Operation Iraqi Freedom/Operation Enduring Freedom/Operation New Dawn [OIF/OEF/OND]), many service members have been exposed to high-intensity blasts, which often cause traumatic brain injuries (TBI). The Department of Veterans Affairs estimates the prevalence of TBI in the OIF/OEF/OND Veteran population to be 7.8 percent. Many of these blast-exposed Veterans experience multiple post-injury deficits, including auditory processing disorders and cognitive dysfunction. The objective of this study is to use event-related potentials to assess auditory and cognitive processing abilities in this population. Several different types of auditory event-related potentials (AERPs) were used to evaluate Veterans who were exposed to high-intensity blasts during military service within the last 10 years. AERPs included auditory brainstem responses (ABRs) to click stimuli and long-latency responses to tonal, dichotic and speech stimuli. Responses recorded from blast-exposed Veterans were compared with responses from age-matched and older control subjects who have not experienced neurological injuries. ABRs from the subject population did not differ significantly from those recorded from control subjects. This suggests that auditory processing at the level of the brain stem was not affected by blast exposure. However, long-latency AERPs recorded from blast-exposed Veterans had greater latencies and smaller amplitudes compared to those recorded from age-matched control subjects. These electrophysiological results are consistent with behavioral deficits in auditory and cognitive processing exhibited by the injured Veterans. Abnormal long-latency AERPs recorded from blast-exposed Veterans might indicate damage to cortical structures and networks responsible for higher-level auditory and cognitive processing. Unfortunately, these deficits persist for many years after the initial injury, which could accelerate the aging process of some affected brains.

Key words
auditory brainstem response, auditory processing, event-related potentials, N200, P300

B3-06

VISUAL PRIMING ENHANCES THE EFFECTS OF NON-SPATIAL COGNITIVE REHABILITATION TRAINING ON SPATIAL LEARNING AFTER EXPERIMENTAL TBI

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Our previous work shows spatial (explicit) and non-spatial (implicit) elements involved with place learning in the Morris water maze (MWM) task can be dissociated and examined in the context of experimental traumatic brain injury (TBI). Also, the provision of non-spatial cognitive training (CT) post-TBI improves place learning versus untrained injured controls. Visual priming strategies are known clinically to facilitate implicit learning. Thus we hypothesized that a *non-contextualized*, brief exposure to extra-maze cues, in conjunction with non-spatial cognitive training, may further improve MWM performance and extra-maze cue utilization compared to non-spatial training (no extra-maze cues priming). Adult male Sprague-dawley rats (n=66) received controlled cortical impact (CCI) injury or sham surgery. Beginning d8 post-surgery CCI and Sham rats were exposed for 6d to no training (NT) or cognitive training with/without brief non-contextualized exposure to extra-maze cues (CT versus BE). Acquisition trials (D14-18), Visible Platform (VP) (D19), and carryover [D20-26)] trials were performed. Platform latencies and time spent swimming the pool peripheral zone were assessed. CCI-BE rats outperformed CCI-NT ($p<0.001$) and CCI-CT rats ($p=0.054$) with acquisition trial latencies. Major latency reductions for CCI-BE versus CCI-CT occurred D14-D15 ($p<0.001$ both comparisons). CT reduced peripheral zone swimming for CCI rats, but BE did not further reduce swimming beyond the effects of CT. No differences with VP or carryover trials were identified for CCI-BE versus CCI-CT, though CCI-NT rats performed similar to CCI-CT/BE rats during carryover trials. These data suggest that visual priming may increase CT effectiveness for initial place learning performance in the MWM, and suggest visual priming response as another translationally relevant experimental rehabilitation construct from which to assess aging and sex differences, as well as pharmacotherapies on cognition after TBI.

Key words
cognitive training, traumatic brain injury, visual priming

B3-07

DIFFERENCES IN SYMPTOM SEVERITY IN MTBI PATIENTS WITH AND WITHOUT PTSD

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The objective is to examine differences in symptoms endorsed by mTBI patients who screen positive for post traumatic stress (PTSD) versus those who do not.

Service members (n = 139) returning from Iraq and Afghanistan receiving care in a 4-week intensive program at the National Intrepid Center of Excellence were evaluated for neurological deficits using the Neurobehavioral Symptom Inventory (NSI), PTSD using the PTSD Checklist Military (PCLm), and measure of effort using the Medical Symptom Validity Test (MSVT). The population was 95.7% male, 36.20 ± 8.3 years old, 14.78 ± &.64 years in service, and 2.4 ± 0.7 number of military deployments. All were > 6 months from last TBI. PCLm total score (≥ 44) and presence/absence of DSM-IV criteria for PTSD defined the PTSD positive group (PTSD+; N = 92) and a PTSD negative group (PTSD-, N = 47). NSI data were then compared across groups. The top five symptoms endorsed by each group were nearly identical: Forgetfulness ($M = 3.01$, $SD = 0.94$), Difficulty sleeping ($M = 2.89$, $SD = 1.10$), Irritability ($M = 2.88$, $SD = 0.94$), Poor concentration ($M = 2.79$, $SD = 0.95$), and Slowed thinking ($M = 2.59$, $SD = 1.06$). PTSD+ and PTSD- groups were compared for individual NSI symptoms, and NSI factors (3 factor model: Somatic/Sensory, Cognitive, & Affective; 4 factor model: Physical, Cognitive, Affective, & Sensory).

Results showed that the differences between 19 of the 22 individual NSI symptoms were statistically significant. Both NSI factor models were significantly different between the PTSD+ and PTSD- groups. Results show that while forgetfulness, difficulty with falling sleep, irritability, poor concentration, slowed thinking, and headache are the top symptoms endorsed by both groups, the PTSD+ group had significantly greater severity of symptoms.

These findings suggest that PTSD+ and PTSD- patients have similar symptoms, but that PTSD+ patients report greater severity. It further supports that, although the presence of psychological comorbidity can worsen perceived symptoms following TBI, symptoms from TBI alone can account for chronic disability in our service members.

Key words
military, NSI, PTSD, trauma

B3-08

CONTROLLING CONFOUNDING EFFECTS IN MTBI VISUAL TRACKING ASSESSMENT

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Attention can be impaired by mild traumatic brain injury (mTBI). We have previously identified that attention impairments associated with mild traumatic brain injury (mTBI) may be detected by quantifying the performance of predictive visual tracking and comparing against population norms. However, there may be confounding personal traits that produce variations in performance norms, which interfere with detection of abnormalities. We sought to better delineate the effects of mTBI on visual tracking by considering factors that may influence performance.

Eye movements during a circular visual tracking task were characterized with indices of gaze-target synchronization and binocular coordination. Possible influences of age and gender on these indices were examined in the data from 139 normal adult subjects. Performance characteristics of 9 patients with mTBI (tested 2 to 55 days post-injury) were compared to the norms.

Within normal subjects, age (18–74 years) was not found to affect performance but male gender was associated with higher smooth pursuit velocity gain. Gender-adjusted norms changed the patients' relative percentile standings such that, given similar smooth pursuit velocity gains, the performance of a male patient can indicate a greater deficit than that of a female patient.

The sensitivity of visual tracking indices to detect differences from the norm needs to be adjusted for gender. Identification of other factors that predict different performance norms is important. *Support: W81XWH-08-1-0646, James S McDonnell Foundation.*

Key words
assessment, concussion, neurocognitive outcome, ocular pursuit, post-concussive syndrome, screening

B3-09

DISPLAY ENHANCED TESTING OF COGNITIVE IMPAIRMENT AND MILD TRAUMATIC BRAIN INJURY (DETECT): A NOVEL TOOL FOR CONCUSSION ASSESSMENT

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Concussion remains difficult to diagnose due to the heterogeneity of the injury and individual responses. Furthermore, current concussion assessment methods are generally subjective and lack validation and standardization. We developed a novel portable neuropsychological platform—Display Enhanced Testing for Cognitive Impairment and Traumatic Brain Injury (DETECT)—to deliver abbreviated, objective neurocognitive tests under immersive conditions to assess reaction time and working memory. We used DETECT to assess cognitive function in two high school and two college football teams over the course of a season (n = 131 subjects). Players were administered baseline DETECT tests and tested immediately following suspected concussions. During the study, 14 subjects had confirmed head impacts and were diagnosed with concussion by a certified athletic trainer or team physician. Choice reaction time, measured using a shape recognition task, was longer post-concussion as compared to baseline (95% mean CL: 0.1, 6.9; p = 0.05); moreover, concussed subjects were less accurate on this task (mean percent correct decrease of 6.1%; 95% mean CL: −10.9, −1.3; p = 0.02). Performance on delayed word recall after a concussion also worsened compared to baseline (mean percent correct decrease of 8.7%; 95% mean CL: −15.5, −1.8; p = 0.02). Further data analysis is in progress and will examine other performance metrics within DETECT across all subjects. DETECT may offer a substantive advancement in the ability to offer a more sensitive sideline tool for cognitive assessment following suspected concussion in athletes as well as other situations where prompt objective cognitive triage is needed. Funded by DoD W81XWH-12-C-0203.

Key words
athletics, concussion, mTBI, neurocognitive, neuropsychological test, reaction time

B3-10

EFFECTS OF FRONTAL TBI ON SIMPLE RESPONSE REQUIREMENTS IN RATS

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Previous work has suggested that operant chambers may provide sensitive assessments of function following TBI. However, TBI may alter basic functions that have wide-ranging effects across reinforcement-based tasks. Simple schedules of reinforcement have been used to evaluate basic changes in function for many years in the fields of experimental analysis of behavior and behavioral pharmacology. These have not been widely explored following TBI and never in a model of frontal injury. Schedules of reinforcement evaluate how a response changes when the requirement for the reinforcer is increased or decreased.

The current study evaluated the lever-pressing performance of sham versus frontal TBI rats on fixed ratio, variable ratio, fixed interval and variable interval schedules of reinforcement. Behavior was conducted in standard operant chambers. Frontal injury was induced using controlled cortical impact centered at +3.0, 0.0 mm from bregma, to a depth of −2.5 mm at a velocity of 3 m/s. Rats were then tested on successive sessions of fixed ratio values 1, 3, 5, 10 and 20. This was followed by variable ratio at the same values. Following ratio testing, fixed interval testing occurred with values of 5, 15, 30, 60 and 120. Variable interval followed at the same values.

There were no large differences in injured versus sham performance in terms of total number of reinforcers obtained or overall efficiency at completing the schedule on any of the schedules tested. Response rates were also similar across the groups.

The relative lack of impairment in injured rats shows that these very basic behavioral functions are still intact following TBI. These results bode well for the evaluation of more complex function using more complicated behavioral measures. Future studies can use these basic building blocks to design more complex tasks to assess cognitive functioning following frontal TBI.

Key words
behavior, cognition, controlled cortical impact, reward/reinforcement, TBI

B4-01

ACUTE CARE AFTER PEDIATRIC TRAUMATIC BRAIN INJURY: A QUALITATIVE STUDY OF THE FAMILY PERSPECTIVE

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Previous studies have linked high quality patient and family centered care to improved patient outcomes, family satisfaction and decreased health care costs. Specific factors associated with quality care for pediatric patients with traumatic brain injury (TBI) have not been identified. This study aimed to explore the family experience of acute care after pediatric TBI to 1) identify specific factors and barriers associated with high quality care unique to this population and 2) develop a model of quality acute care. We conducted in-depth interviews with 15 parents of patients who were < 18 years old and who had an acute hospital stay within the last 5 years. English, Spanish and Cantonese speaking families were recruited from 2 large, urban trauma centers. Interviews were transcribed verbatim and qualitative content analysis was used to develop a taxonomy of domains and factors associated with quality patient and family centered care. Three major domains associated with high quality care were identified: 1) thorough, timely and compassionate communication, 2) capacity building for families and providers, and 3) coordination of care transitions. Parents reported valuing detailed, frequent and understandable communication that set realistic expectations and prepared them for decision-making and outcomes. They identified areas for capacity building including methods to increase parent participation in care and strategies to increase provider cultural humility and institutional flexibility. Coordinated care transitions were highlighted as important, especially continuity of information and maintenance of partnerships with families and new care teams. Understanding the family perspective and integrating it into practice are important steps to improving patient outcomes. Results from this study will be used to inform development of new care pathways for pediatric TBI patients.

Key words
acute care, family perspective, pediatric traumatic brain injury, qualitative study

B4-02

PLAYGAME: A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL OF MELATONIN FOR THE TREATMENT OF POST CONCUSSION SYNDROME IN YOUTH

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Fourteen percent of school-aged children with mTBI have post concussion syndrome (PCS) for at least 3 months. PCS is associated with significant disability in children and burden on families, and yet there are no evidence-based medical treatments available. Although Melatonin is best known for its chronobiological actions, its therapeutic potential is being explored in neurobehavioural conditions such as headache and anxiety. Biological activities of melatonin are both receptor-mediated (at physiological levels) and non-receptor mediated (especially at supraphysiological levels). Proposed neuroprotective mechanisms include decreasing oxidative damage, improving mitochondrial function and decreasing the neuroinflammation.

The aim of this study is to determine if Melatonin improves PCS following mTBI in youth.

Does the treatment of children with PCS symptoms following mTBI with 3mg sublingual melatonin or 10mg of sublingual melatonin for 28 days result in a decrease in PCS (physical, cognitive and behavioural) symptoms as compared with placebo?

Is there a dose-response relationship?

Is the treatment effect independent of the effect on sleep?

This study will be conducted as a randomized, double blind, placebo controlled trial. Three parallel treatment groups will be examined: 1) sublingual placebo, 2) sublingual melatonin 3mg, and 3) sublingual melatonin 10mg. The design allows for dose dependent response assessment. This is a single center study which will

recruit participants over 3 years, with a second center coming online in years 4 and 5.

Target population: Children aged 13 to 18 years with mTBI who remain symptomatic at 30 days post-injury.

The mechanisms of action of melatonin relevant to mTBI and PCS in youth will be presented, together with results of a case-series of children with PCS treated with melatonin. The PLAY-GAME trial, which began enrolment in November 2013 will be presented.

Key words
melatonin, mild traumatic brain injury, neuroprotection, post concussion syndrome

B4-03

EFFECT OF A COMMUNITY EDUCATION PROGRAM ON PEDIATRICIAN'S MANAGEMENT OF CONCUSSIONS

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Although pediatricians frequently manage concussions, they often feel ill-equipped to execute treatment, possibly due to inadequate training, lack of universally accepted guidelines, and misconceptions regarding concussion management. Here, we implemented community-wide, comprehensive education on concussion management and aimed to evaluate its impact on practice and attitudes in concussion management.

A comprehensive evidence-based educational curriculum on concussion management was established through a concussion program at a tertiary teaching hospital. In June, 2012, web-based education and lectures were provided on definitions, symptoms, emergency/specialist referral, and CT scanning. Pre-program surveys were distributed to 614 pediatricians in May, 2012, and post-surveys were distributed 18 months later (Oct, 2013) to 619 pediatricians. We analyzed overall knowledge, comfort level in managing concussions, ability to manage various head injury scenarios, and understanding of management options. Data were analyzed using Chi-square tests.

Overall, 204/614 and 157/619 pediatricians responded to the pre- and post-surveys, respectively. Pre- to post-survey, pediatricians reporting 'comfortable' or 'very comfortable' managing concussions increased from 71.6% to 84.1% (146/204 to 132/157; $p < 0.01$). Use of guidelines to manage concussions increased from 59.3% to 91.0% (121/204 to 142/156; $p < 0.001$). Pediatricians advising gradual return to play after a concussion increased from 39.7% to 64.7% (81/204 to 101/156; $p < 0.001$).

Implementing a concussion education program for pediatricians improved self-reported practice and attitudes on managing children with concussions, including comfort level and use of guidelines and evidence-based strategies. This has implications on reducing unnecessary short-term interventions and optimizing longer-term outcomes via safer return to play.

Key words
community education, concussion, mild traumatic brain injury, pediatrician

B4-04

MATRIX METALLOPROTEINASES AS THERAPEUTIC TARGETS FOR THE INJURED PEDIATRIC BRAIN

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Matrix-metalloproteinase (MMP)-9 and −2, are destructive proteolytic enzymes and key mediators of damage in adult traumatic brain injury (TBI). Their involvement in the injured pediatric brain has to be determined. In the pediatric brain, we found upregulation of pro-MMP-9 and pro-MMP-2 by gelatin zymography within the first 48 hours post-injury. To determine the contribution of these gelatinases to long-term recovery, male mice subjected to TBI at postnatal day 21 were treated acutely with *p*-OH-SB-3CT, a potent gelatinase inhibitor, or vehicle and evaluated at adulthood. Both groups showed similar long-term functional impairments (hyperactivity, deficits in learning and spatial memory, and sociability), neuronal and tissue loss. In light of these findings, we examined indices of cell death in the acutely injured brain. Immunofluorescence displayed equivalent levels of TUNEL and caspase-3 in both groups. Such findings prompted a more extensive profiling of actively expressed MMPs in the acutely injured brain. A newly developed assay to identify and quantify active MMPs and related proteins revealed no active forms of MMP-9 and −2 but rather active MMP-19 and a disintegrin and metalloproteinase domain-containing protein (ADAM)-9 and ADAM-10, with ADAM-10 significantly increased after TBI and unaffected by treatment. These results demonstrate a unique profile of MMPs and ADAMs in the acutely injured immature brain, a finding that contrasts the dominant role of MMP-2 and −9 in the injured adult brain. Such findings underscore the concept that the developing brain shows acute injury-related responses that are unique from those of the injured adult brain. Thus, understanding the processes of long-term structural and functional recovery after pediatric TBI is contingent upon a broader profiling of the acute injury-response to precisely delineate those pathogenic targets that are determinants of long-term recovery.

Funding:NINDS-R01NS050159

Key words
cognitive behavior, developing brain, gelatinases, MMP, traumatic brain injury

B4-05

EMOTION PROCESSING FOLLOWING PEDIATRIC TRAUMATIC BRAIN INJURY

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Children with traumatic brain injury (TBI) often have difficulty in the domains of behavioral control and social skills, including difficulty identifying the emotional state and intentions of other people. We investigated whether children with TBI also have difficulty ascertaining emotional state from facial cues, which may also prompt errors in attribution of intention in others.

Participants included 57 children between the ages of 8 and 16 years of age split into three groups: traumatic brain injury ($n = 23$),

extra-cranial injury (n = 13), and typically developing controls (n = 21). Age did not differ between the groups. Participants completed a battery of psychological measures which included a novel Emotional Go/No-Go task. Injury groups completed the battery six weeks post-injury. The Emotional Go/No-Go task included photographs of happy, neutral, and fearful facial expressions. On each subtask, participants were given a Go emotion and had to make judgments between facial expressions with either the Go emotion or one of the other two emotions in a pseudo-counterbalanced presentation with 6 individual subtasks.

General Linear Models compared performance on the Emotional Go/No-Go task. There were no group differences in accuracy, $F(2,54) = 1.89$, $p = 0.16$, or reaction time, $F(2,54) = 0.25$, $p = 0.78$, on overall performance. However, in a repeated measures model of false recognition errors, there was a significant interaction between the three Go emotions and group, in which the TBI group made significantly more false recognition errors when the Go Emotion was fear than the other two groups $F(4,108) = 2.76$, $p = 0.03$. There were no group differences on false recognitions of the other two Go emotions.

Children with TBI demonstrated increased error rates for falsely recognizing an emotion as fear in others at six weeks post-injury. This suggests a possible underlying deficit in reading of social cues, particularly those involving anxiety, which may have significant impact on emotion regulation. Future study will focus on determining the longitudinal course and consequences of this deficit.

Key words
emotion processing, emotional go/no go, fear, social cognition

B4-06

SLEEP DISTURBANCE IN SPORTS RELATED CONCUSSIONS IN CHILDREN

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The objective of this study was to illustrate any symptoms associated with sleep disturbances and also to explore potential benefits of using a graded symptom checklist in identifying sleep disturbances in children following sports related concussions.

Data was retrospectively collected from 126 patients (age 5–22; mean age 14.THOD7) who presented to the pediatric TBI clinic at UCLA between years 2005 and 2013. For each patient, presence of various symptoms, including sleep disturbance, was determined by reviewing the HPI, and for a subset of patients (33/126), the graded symptom checklist (GSC) was also used to determine the presence of symptoms.

Sleep disturbance was associated with cognitive problems ($p = 0.03$) and fatigue ($p < 0.01$), but not with headache ($p = 0.06$), pain other than headache ($p = 0.12$), or emotional problems ($p = 0.23$). Compared to patients without sleep disturbance, patients with sleep disturbance scored worse on GSC (11.18 vs 39.25; $p < 0.01$ CI −40.50 to −15.63), standardized assessment of Concussion (SAC) (28.8 vs 25.28; $p < 0.01$ CI 2.04 to 5.00), and computerized reaction time (0.54 vs 0.77; $p = 0.01$ CI −0.41 to −0.06). Patients were more likely to report symptoms of headache (OR 3.03 $p = 0.02$ CI 1.20 to 8.90), pain other than headache (OR 11.38 $p < 0.01$ CI2.49 to 88.18), cognitive problems (OR 11.95 $p < 0.01$ CI 3.87 to 54.57), and emotional problems (OR 9.57 $p < 0.01$ CI3 3.99 to 24.75) with use of the GSC compared to without, but the greatest increase in likelihood were seen in fatigue (OR 23.22 $P < 0.01$ CI 8.43 to 72.37) and sleep disturbance (OR 20.18 $p < 0.01$ CI 7.52 to 60.21).

Sleep disturbance was common in children following sports related concussions and was associated with multiple comorbidities including cognitive problems, fatigue, and poorer performances on the GSC, SAC, and computerized reaction time. When identifying post-concussion symptoms, using the GSC was especially beneficial in identifying additional cases of sleep disturbances compared to other symptoms.

Supported by
UCLA BIRC, NS05489, HD061504, Friends of Semel, Child Neurology Foundation/Winokur Family Foundation, Jonathan Drown Foundation, Today's and Tomorrow's Children Fund.

Key words
graded symptom checklist, sleep disturbance, sports related concussion

B4-07

EFFECT OF TBI ON RNA BINDING MOTIF 5 (RBM5) AND 3 (RBM3) PROTEIN EXPRESSION IN THE DEVELOPING RAT BRAIN

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RBM family proteins regulate messenger RNA (mRNA) processing, intracellular localization, and stability. The pro-death protein RBM5 regulates exon splicing of target mRNAs. Modulation of caspase-2 splice variants is a prime example. RBM5 up-regulates expression of pro-death caspase-2L (long) but decreases pro-survival caspase-2s (short). RBM3 is a cold-inducible and pro-survival protein that regulates mRNA stability. RBM3 was recently reported to induce neuroprotection *in vitro*. Here we examined protein changes in brain RBM5 and RBM3 after TBI in developing rats. Postnatal day 17 (PND17) Sprague Dawley rats were subjected to controlled cortical impact (CCI) traumatic brain injury (TBI). Shams received surgery without CCI. Cortex/hippocampus (ipsilateral to injury) was harvested for biochemistry 24 h later. Brain tissue was also harvested from rat (E17) embryos, naïve PND17, and adults; to define developmental expression of RBM5/RBM3. RBM5 reportedly migrates at ~120KDa and ~90KDa on SDS-PAGE. RBM5 protein expression decreased with age. The ~120KDa form was highest in embryonic brain and lowest in adults. The ~90KDa form was highest in embryonic and PND17 brain. RBM3 reportedly migrates at ~17KDa. RBM3 was abundant in embryonic brain, low in PND17, and undetectable in adults. TBI induced a significant decrease of ~90KDa RBM5 in cortical/hippocampal tissues harvested 24 h after injury. The ~120KDa RBM5 protein did not significantly differ after injury compared to naïves. In contrast, RBM3 significantly increased in injured cortical/hippocampal tissue 24 h after TBI. Conclusions: Here we report that the pro-death splicing factor RBM5 is down-regulated in a model of pediatric TBI. In contrast, the pro-survival protein RBM3 increases in cortex/hippocampus after brain injury. Taken together our findings suggest that RBM5/RBM3 proteins are abundant in developing brain. Changes in protein levels after CCI may represent an endogenous neuroprotective response in young rats. RBM5 and RBM3 represent potential targets that merit further exploration in both developmental and adult TBI. This work was supported in part by US Army grant W81XWH-10-1-0623.

Key words
biochemistry, controlled cortical impact, RNA binding motifs, therapeutics

B4-08

REPETITIVE MILD TRAUMATIC BRAIN INJURY IN THE IMMATURE BRAIN

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Repetitive traumatic brain injury (TBI) occurs in unique pediatric conditions, such as abusive head trauma (AHT) and sports concussion. While accumulating evidence suggests that repeated mild TBI (rmTBI) may cause long-term cognitive dysfunction in adults, it is unknown whether rmTBI causes similar deficits in the immature brain. We studied the effect of rmTBI in immature brain on acute and chronic histological and neurocognitive outcome. 18d-old rats were divided into two groups. The 1st (n = 3/grp) received either two closed head impacts (CHI, 9.5mm rubber tip impactor, 4m/s velocity, 1mm depth), one CHI paired with sham (S) or two sham (S/S) insults 24 h apart. Histology at 7d included silver staining to detect axonal injury, Iba-1 immunohistochemistry to assess microglial activation, H&E to evaluate cell survival. The 2nd group received three CHI (n = 18) or three sham insults (n = 12) 24 h apart and evaluated for motor [beam balance (BB); inclined plane (IP) tests, d1-5] and cognitive [Morris water maze (MWM; d11-15, 60); Novel Object Recognition (NOR; d18); Elevated Plus Maze (EPM; d90); and Fear Conditioning (FC; d92)] dysfunction. Silver staining revealed argyrophilia and axonal staining in the ipsilateral external capsule of CHI/S and CHI/CHI groups. H&E staining showed no overt neuronal loss. Second impact increased axonal staining in ipsilateral external capsule. Increased Iba1 positivity with morphological appearance of activated microglia was observed in bilateral amygdala after CHI/S and CHI/CHI. There were no differences in BB, IP, MWM and EPM performance between groups. However, rmTBI rats were impaired in the NOR ($P < 0.05$, 66 ± 2.4 vs $75 \pm 4\%$) and froze less than sham to a context ($P < 0.05$, 89 ± 3.4 vs $99 \pm 0.3\%$) or a discrete auditory cue ($P < 0.05$, 26.4 ± 5.9 vs $44.9 \pm 8.4\%$). In conclusion, rmTBI amplifies the mTBI response producing diffuse axonal injury, microglial activation and memory deficits. This model could be useful in therapy development for AHT or sports concussion in children. Support: NS061817, U19AIO68021, NS076511

Key words
abusive head trauma, immature brain, repetetive mild traumatic brain injury, sport concussions

B4-09

NORMAL BACKGROUND OF APOPTOSIS IN JUVENILE RATS USED AS BASIS TO DETERMINE INDUCED DEGENERATION BY THE NEUROTOXIN MK-801

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Degeneration/apoptosis in juvenile brains from PND 0 to PND 24 is minimal to abundant in different brain regions as a function of time. This 'backdrop' of degeneration (DEG)/apoptosis (APO) must be taken into account when assessing possible induction of degeneration by chemical or physical insults. This study sought to determine the relationship of normal changes and the effects of MK-801 (a non-competitive NMDA antagonist with known neurotoxic properties) on the development of juvenile Sprague-Dawley rat brains. The MK-801 group received a single dose (3 mg/kg, IP) on PNDs 7, 8, 9, 11 13, 16, 23, 39, 69 or 111). Distilled water was the control article. Thirty or twenty rats per sex per time-point had brains perfused/harvested on PNDs 8, 9, 10 and 12, or on PNDs 14, 17, 24, 40, 71 and 113, respectively. The brains were MultiBrain® embedded, coronally sectioned at 40μ and 1/8th section stained with the amino cupric silver method (DEG changes) and activated caspase 9 immunohistochemistry staining (APO). APO and DEG were prevalent in numerous brain regions of younger control animals (primarily from PND 8 through PND 24). Increased DEG and APO were present in MK-801 animals at all time-points. Increased DEG and APO in MK-801 rats were present in a large number of brain sites in the earlier PNDs with severities ranging from minimal to marked while these changes at later PNDs were substantially diminished. Females had more brain sites involved than did males especially at the later PNDs. By PND 40, males had only 3 or 4 sites at which DEG was observed. APO that was present in MK-801 rats was distinct and unequivocal when compared with the control animals. Based on this data, isolated minimal or mild occurrences of DEG and APO should not be considered treatment related events in juvenile Sprague-Dawley rats.

Key words
apoptosis, degeneration, juvenile, neonate, trauma

B4-10

EXAMINING D-CYCLOSERINE ADMINISTRATION PROTOCOLS IN DEVELOPING RATS FOLLOWING LFPI AND REDUCING VARIABILITY IN PCAMKII LEVELS

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This study examined the effects of different doses of D-cycloserine (DCS) administration on NMDA 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. Additionally, this study investigated exposing P19 rats to an enriched environment prior to sacrifice in an attempt to decrease the variability of pCaMKII levels in hippocampus through functional stimulation. P19 rats underwent LFPI and received either a single DCS dose (30 mg/kg; 0.25 ml/kg) 24 hours post-injury, 5 DCS doses every 12 hours starting 24 hours post-injury, or saline. We found a significant increase in pCaMKII levels in the 5 injection protocol group when compared to the vehicle ($p = 0.017$), while no significant increase occurred between the single injection and vehicle ($p = 0.188$). Thus, a protocol with multiple injections is more appropriate for further investigation into the therapeutic benefits of DCS following TBI in the juvenile rat. We additionally hypothesized that 20 minutes of novel environment exploration would reduce variability of pCaMKII levels in the hippocampus via activation of NMDA signaling. Four days following craniotomy, subjects were either housed in a new cage with novel objects or returned to homecage for 20 minutes, followed by sacrifice, micro-dissection of hippocampus, and Western analysis. Although no significant difference in pCaMKII levels ($p = 0.772$) was observed between the two groups, the variance was reduced in the group exposed to an enriched environment prior to sacrifice compared to the control group, suggesting a more consistent activation of pCaMKII prior to euthanization. This decreased variability potentially allows for smaller animal groups in future experiments.

This research was supported by UCLA BIRC, NS027544, NS05489, Child Neurology Foundation/Winokur Family Foundation, and the Jonathan Drown Foundation.

Key words
D-cycloserine, FPI, pCaMKII, recovery, severe FPI

B4-11

MODERATE TRAUMATIC BRAIN INJURY (TBI) IN ADOLESCENT MICE ENHANCES COCAINE-INDUCED PLACE PREFERENCE

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Clinical evidence indicates a connection between traumatic brain injury (TBI) and addictive tendencies; however, very few pre-clinical studies have been performed to understand the effect that brain injury may have on drug addiction. Therefore, we designed a pilot study to test the hypothesis that TBI exacerbates the reinforcing properties of cocaine in a biased, conditioned place preference (CPP) assay. Adolescent, six-week old C57BL/6 mice underwent craniotomy surgery, after which the mice sustained a single, moderate TBI (speed: 4.5 m/s, depth of impact: 2.0 mm, dwell time: 0.5s) to the right parietal somatosensory cortex using an electromagnetically driven piston (diameter: 2.0 mm). One-week post-TBI, an activity-monitoring assay was used to assess locomotor deficits arising as a result of surgical/impact procedures. Impacted animals showed no locomotor deficits when compared to adolescent control subjects. CPP pre-testing occurred 2 weeks post-TBI, followed by six days of non-contingent cocaine administration (10 mg/kg) through intraperitoneal injection. The place preference shift in the drug-paired environment was significantly enhanced in all treatment groups receiving cocaine as compared to saline controls. Furthermore, mice sustaining a moderate TBI during adolescence exhibited a significant increase in cocaine-induced place preference as compared to uninjured controls receiving cocaine. These results suggest that adolescent mice sustaining a single, moderate TBI may be increasingly susceptible to the reinforcing properties of cocaine.

Key words
behavioral assay, controlled cortical impact, drugs of abuse, glia, mesolimbic

B4-12

ACETYL-L-CARNITINE IMPROVES METABOLIC DYSFUNCTION AND BEHAVIORAL OUTCOME AFTER TRAUMATIC BRAIN INJURY IN IMMATURE RAT

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Traumatic brain injury (TBI) is the leading cause of permanent life-long disability in children and is characterized by deficits in cognition, attention and sensorimotor integration. Depressed glucose cerebral energy metabolism is attributed to mitochondrial dysfunction following pediatric TBI. Developing brain is able to utilize alternative substrates and support energy and metabolism by using ketones and fatty acids. Acetyl-L-carnitine (ALCAR) is an endogenous metabolic intermediate that provides acetyl moiety directly to the citric acid cycle, as well as carnitine - which is essential for transport of fatty acids across the mitochondrial membrane for β-oxidation. This study tested the hypothesis that treatment with exogenous ALCAR in the first 24 hrs after TBI improves neurologic outcome and decreases cell death by supporting cell specific (astrocytic) metabolism. Postnatal day 21–22 male rats were isoflurane anesthetized and used in a controlled cortical model (CCI) of TBI to the left parietal cortex. At 1, 4, 12 and 23 hrs after injury rats were treated with ALCAR (100 mg/kg/dose) or vehicle (normal saline). Using Western blot analyses at 6 and 24 hrs after TBI we determined that carnitine palmitoyl transferases (1 and 2), which facilitate mitochondrial β-oxidation, were not decreased in ALCAR treated group. Treatment with ALCAR increased amount of glutamine and gamma-hydroxybutyric acid determined by *in vivo* 1H MRS, decreased lesion volume and cell death and improved behavioral outcome after TBI in developing brain.

Key words
acetyl-L-carnitine, metabolism, neuroprotection, pediatric TBI

B4-13

LONG-TERM BEHAVIORAL CONSEQUENCES EMERGE OVER TIME AFTER CONCUSSIVE INJURIES AT ADOLESCENCE

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There is growing controversy surrounding the management of concussion in young athletes, with evidence suggesting that repeated concussions result in cumulative and chronic neurological impairments associated with neurodegeneration. The adolescent brain may be particularly vulnerable to concussions due to ongoing maturation at this time in the setting of sports-related impacts. Using a unilateral controlled cortical impact to the intact skull of mice at postnatal day 35, we here aimed to characterize the consequences of a single concussive injury or repeated insults (2 impacts, 48 h apart) as the animal matured. At 24 h post-injury, injured brains were negative for markers of cell death (TUNEL or active caspase-3), axonal degeneration (beta-amyloid precursor protein), neuroinflammation (Iba-1 microglia) or gross structural damage (cresyl violet). Further, volumetric analysis of the dorsal cortex and corpus callosum at 3 months post-injury failed to detect any injury-related atrophy, indicating the very mild nature of this insult. Despite this lack of neuropathology, behavioral assessments detected a pronounced hypoactive phenotype in the open field and elevated plus maze, which emerged over time and persisted up to 3 months post-injury, the last time point studied. These changes were observed in the absence of any sensorimotor dysfunction (rotarod; cylinder test) or cognitive deficits (radial arm water maze; novel object recognition), suggesting a hierarchy of behaviors whereby measures of general activity are most sensitive to the mildest forms of concussion. Of note, both single and repeated injuries at adolescence produced a similar

profile of functional deficits. These data highlight the vulnerability of the adolescent brain to even a single concussive insult which does not produce pathological hallmarks traditionally associated with brain injury. Ongoing studies aim to evaluate whether reduced activity reflects changes in depressive or anxiety-like behaviors. Support: Private donor.

Key words
adolescence, behavior, concussion, hypoactivity, mild brain injury

B4-14

PEDIATRIC POST-CONCUSSION SYMPTOMS ARE ASSOCIATED WITH REDUCED CORTICAL COMMUNICATION AS DETECTED WITH NEAR-INFRARED SPECTROSCOPY

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Traumatic brain injury (TBI) is the leading cause of injury under the age of 25. Its pathophysiology is poorly understood and it is difficult to detect with standard imaging methods. Functional near-infrared spectroscopy (fNIRS) is an inexpensive and portable technology with high temporal resolution, and can detect changes in hemoglobin associated with cortical brain activity. This project aimed to determine if fNIRS could detect reduction in functional coherence in pediatric mTBI patients with chronic symptoms as a marker of impaired interhemispheric communication associated with brain injury.

Twelve patients (age 15.2 ± 1.9 years, six males) with chronic mTBI symptoms (average time since injury = 179 days) and eight healthy control subjects (age 14 ± 2.2, five males) were recruited. Using a continuous wave mapping system (CW5, TechEn, Inc., Milford, MA), fNIRS data were recorded from the motor cortices for five minutes each of rest, and finger tapping task activation. Data from the source-detector pair over the left hemisphere that exhibited the greatest increase in oxyhemoglobin during finger tapping was taken as a frequency reference for coherence analysis. Values were averaged over each of the ipsilateral and contralateral hemispheres.

During finger tapping there was no difference in magnitude of activation of total and oxy-hemoglobin. Resting-state coherence did not differ between mTBI patients and controls. Coherence for mTBI was initially lower in all parameters except in the ipsilateral side during task activation. Coherence during finger tapping was significantly reduced for mTBI patients in both the ipsilateral ($p < 0.01$) and contralateral ($p < 0.001$) hemispheres, compared with controls.

Reduced coherence between the motor cortices is consistent with impaired communication and may reflect damage to communicating fiber tracts. fNIRS provides a new non-invasive method to study brain functional impairment associated with mTBI. The study illustrates chronic functional impairments following mTBI's and further studies should investigate whether coherence continues to be altered with symptom resolution.

Key words
brain connectivity, concussion, mild traumatic brain injury, near infrared spectroscopy

B4-15

MIDLINE FLUID PERCUSSION INJURY IN THE DEVELOPING RODENT RESULTS IN DIFFUSE INJURY AND DEVIATION OF THE NEUROVASCULAR UNIT

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Juvenile diffuse traumatic brain injury (jTBI) leaves survivors facing a lifetime of potential neurological symptoms. Pathology across the neurons, glia and vasculature of the neurovascular units (NVU) likely underlie the symptomatology and serve as potential therapeutic targets. We hypothesize that diffuse jTBI in the rat (post-natal day 17) results in a deviation of the NVU from the natural development in uninjured animals over 28d post-injury and across brain regions. Moderate jTBI was induced by midline fluid percussion injury (1.4atm) and verified by the clinical endpoints of righting reflex suppression, seizure and apnea. Unlike in older rats, righting reflex was inconclusive in juveniles, but 87% experienced seizures (72 ± 9s), and 77% experienced apnea (31 ± 7s). All brain-injured animals presented with hematoma and herniation, followed by stunted weight gain, evident through 28d post-injury. At 2 h, 1d, 7d, and 28d post-injury, tissue was examined for components of the NVU. Similar to MRI following clinical diffuse injury, H&E staining confirmed jTBI without overt damage or cavitation. IgG extravasation showed vasculature damage in the cingulate and motor cortices indicating permeability of the blood brain barrier at 2 h and 1d with resolution by 7d post-injury. Astrocyte (GFAP) and microglia (Iba-1) activation were observed following injury in the same regions as IgG and returning to sham-level by 28d post-injury. In conclusion, we have developed a clinically relevant model of diffuse jTBI to investigate neurological deficits associated with the cingulate and motor cortices, while screening therapeutic treatments associated with the NVU.

Funding: PCH Mission Support Funds

Key words
diffuse brain injury, midline fluid percussion injury

B4-16

ELECTROPHYSIOLOGICAL SIGNATURES OF JUVENILE MILD TRAUMATIC BRAIN INJURY DURING NOVEL OBJECT RECOGNITION

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Mild traumatic brain injury (mTBI) acquired through various civilian and military impacts affects ~40% of 1 million juvenile patients annually in the USA. Despite numerous studies on neuroplastic changes caused by a single incidence of mTBI, few have attempted to directly correlate the longitudinal process of functional recovery with repeat performance at a hippocampally-centered working memory task. We studied concurrent behavior and electrophysiology in juvenile, male Sprague-Dawley rats implanted with four hippocampal electrodes and a miniature extra-cranial wireless transceiver system to elicit cross-frequency coupling in local field potentials (LFPs) and thus establish the signature of injury. We monitored untethered animals demonstrating stereotypical behaviors during repeated assignments of the stressor-free novel object recognition (NOR) task during three weeks following fluid-percussion injury at PND35, compar-

ing them within subject and injury-group to pre-implant/injury baseline behavior.

Whereas our previous work based solely on behavior of adult subjects showed no cognitive recovery upto PID17, this study of juveniles (5 naïve, 4 sham-implanted, 4 mTBI-implanted) shows prospect of behavioral recovery by PID17 ($p = 0.248$) without such effects at PID3 ($p = 0.001$) or PID10 ($p = 0.039$), relative to pre-injury behavior at PND31. Comparing novel object preference against naïves we find limited injury due to implantation alone (mTBI-implanted $p = 0.015$; sham-implanted $p = 0.0578$). Following exclusion of electro-mechanical interferences, cross-frequency power maps (4–40) Hz spanning theta and low-gamma ranges, indicate aperiodic changes in concurrency from electrode located nearest FPI site (Left-Anterior) with neighboring (Right-Anterior and Left-Posterior) sites in injured subjects during routine exploration and during object approach relative to shams.

We hypothesize (**H_1[1]**) that mildly injured (loss-of-consciousness < 45s) PND35 rats demonstrate partial recovery of working memory by adulthood (PND52). We additionally hypothesize (**H_1[2]**) that such recovery does not occur in moderately or severely injured juveniles (loss-of-consciousness > 45 sec). Evidence in the form of cross-frequency concurrency maps, correlated with real-time stereotyped behaviors during stages of NOR, will be presented. This research was supported by NSF ECCS-0847088, UCLA BIRC, NS027544 and NS05489.

Key words
concurrency, cross-frequency, injury signature, mote, wireless

B4-17

NEUROLOGICAL DEFICITS FOLLOWING TRAUMATIC BRAIN INJURY IS AFFECTED BY AGE AND SEVERITY OF INJURY IN PART DUE TO MYOSIN LIGHT CHAIN KINASE INTERACTING WITH ISG15

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Recent studies have shown that MLCK (Myosin light chain kinase) plays a pivotal role in development of cerebral edema, a known complication following TBI in children and a contributing factor to worsened neurologic recovery. Lately, increased levels of ISG15 an ubiquitin-like protein, has been seen after global ischemia, focal ischemia, and are neuroprotective. The significant role of ISG15 after TBI is not yet studied.

PND21 and PND24 ($n = 6$ per group) 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). Neurological outcome was examined at 7d with two-object novel recognition and wire hang tests. Mice were sacrificed at 6, 12, 24, 48, 72 h and 7d. ISG15 and MLCK analyzed by western blot, immunohistochemistry; BBB disruption with Evans Blue (EB) and wet/dry weights.

Two-object novel recognition: Number of touches: novel vs. old objects, PND21 (2.00 mm: 12.92 vs. 13.33 and 2.25 mm: 36 vs. 66, respectively) PND24 (2.00 mm: 31 vs. 42 and 2.25 mm: 40 vs. 60, respectively).

Wire hang-motor test: Latency to fall in seconds (s): PND21: 2.00 mm: 21s, 2.25 mm: 2s. PND24 2.00: 14s, 2.25: 5s.

ISG15 upregulation: PND21 normalized to actin (pixel density) 12 h 2.00 mm: 1.539, 2.25 mm: 1.889 and 72 h 2.00 mm: 1.349, 2.25 mm: 2.659. PND24 6 h 2.00 mm: 1.774, 2.25 mm: 2.168. Co-localization of ISG15 and MLCK is confirmed by immunohistochemistry.

Wet/dry weights (g): PND21 72 h 2.00 mm: 2.035, 2.25 mm: 2.143, 7 D, 2.00 mm: 1.797, 2.25 mm: PND24 72 h 2.00 mm: 1.842, 2.25 m: 2.47, 7D 2.00 mm: 1.778, 2.25 mm: 1.745.

EB ng/grams of brain: PND21 72 h 2.00 mm: 3074.55, 2.25 mm: 6027.62, 7D 2.00 mm: 1878.771, 2.25 mm: 2927.94. PND24 72 h 2.00 mm: 3045.995, 2.25 mm: 7408.914; 7D: 2.00 mm: 924.623, 2.25 mm: 951.625.

ISG15 is elevated following TBI in PND 21 and 24 mice preceding the elevation of MLCK and the development of BBB disruption and cerebral edema.

Key words
blood brain barrier, immature brain, ISG15, MLCK, TBI

B4-18

NEUROPROTECTIVE MECHANISMS OF DOCOSAHEXAENOIC ACID IN RAT PUPS AFTER TRAUMATIC BRAIN INJURY

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Dietary Docosahexaenoic Acid (DHA) improved white matter injury and cognitive impairment in our rat pup controlled cortical impact (CCI) model of developmental TBI, associated with decreased oxidative stress and inflammation. Mechanisms of DHA's neuroprotection are poorly understood. Microglia, the brain's resident macrophages, mediate oxidative stress and inflammation after TBI. In systemic macrophages, DHA decreases inflammatory (M1) activation while promoting reparatory (M2) activation. Effects of DHA on microglia after TBI are not known.

We hypothesized that DHA would decrease microglial activation and markers of M1 transformation after CCI in the 17 day old rat.

CCI or SHAM surgery was delivered to 17 day old male rats exposed to 0.1% DHA (DHA) or otherwise equivalent chow (REG). TSPO imaging and histology at post injury day (PID) 3 and 50 were done to assess microglial activation and lesion volume. mRNA levels of M1 (IL-1β, IL-12 β, IL-6, IL-18rap, CCL2, INF Y, TNFα, iNOS) and M2 (IL-4, L-1Rα, CD206, IL-10, TGFβ and Arg1) markers were measured in microglia isolated by flow cytometry and in injured tissue at PID 2 and 3.

Preliminary results suggest decreased microglial activation at PID3. DHA decreased M1 marker mRNA IL6 (to 71 ± 4% REGCCI), IL-1β (to 59.6 ± 7%), IL-18rap (49.8 ± 4%), CCL2 (to 18.2 3% ± 3 %), TNFα (to 75 ± 6%) and INF Y (to 51 ± 4%) in PID2 hippocampi ($p < 0.05$). Partial results suggest DHA decreased lesion volume (21.6 vs 29.8% loss, $p = 0.06$) without changing microglial activation at PID50.

Exposure to a 0.1% DHA diet after CCI is associated with decreased M1 activation markers in hippocampus at PID2. Preliminary data suggests DHA decreases microglial activation at PID3 and lesion volume at PID50. We anticipate that DHA will decrease M1 marker mRNA in isolated microglia. We speculate that DHA improves cognitive function after CCI via immunomodulation.

Key words
developmental, docosahexaenoic acid, traumatic brain injury

B4-19

MEMORY AND THE HIPPOCAMPAL FORMATION FOLLOWING PEDIATRIC TRAUMATIC BRAIN INJURY

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The goal of this research was to evaluate the impact of pediatric traumatic brain injury (TBI) on nonverbal memory in relation to volume of the hippocampus, a region of the brain that is critical for declarative memory.

The present study examined children 6 weeks following a mild or moderate TBI (TBI, n = 17) or extracranial injury (EI, n = 16). Additionally, children, without a history of injury, were included as a comparison group (n = 21). Children ranged in age from 8–15-years with a mean age of 12-years for each of the groups.

Non-verbal memory was measured with the Visual Selective Reminding subtest of TOMAL2. Participants were asked to learn a spatial dot pattern over the course of several trials. Scores for each participant were normed for age. Structural brain data were acquired on a Philips 3T MR scanner. Cortical and subcortical volumes were first segmented with Freesurfer and then manually edited to ensure accuracy of anatomy boundaries.

Controlling for total brain volume, a positive correlation was seen between right hippocampal volume and performance on the Visual Selective Reminding task for the TBI group, r14 = 0.56, $p = 0.02$, but not the EI group or the comparison group. In the left hippocampus, controlling for total brain volume, for TBI and EI groups a similar trend was evident indicating that that individuals with larger left hippocampal volumes showed higher scores on the Visual Selective Reminding task (TBI: r14 = 0.45, $p = 0.08$; EI:, r13 = 0.49, $p = 0.06$). This trend was not found in the comparison group.

Previous research indicates disruption of attention and memory in children who have experienced TBI. The results of the current study highlight the relation between hippocampal structure and memory function during the subacute stage of recovery from mild to moderate TBI. Longitudinal follow-up is needed to characterize changes in hippocampal volume and integrity and their relation to the development of memory following TBI.

Key words
childhood, hippocampus, learning, memory

B4-20

THE EFFECT OF BODY CHECKING AND HEAD CONTACT RULE POLICY CHANGES ON CONCUSSION RISK IN YOUTH ICE HOCKEY PLAYERS

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The objectives are 1) To determine if the risk of concussion differ for 11–12 year old ice hockey players in leagues where body checking is permitted compared to leagues where it is not. 2) To examine the effect of 2011 rule enforcement policy change ''zero tolerance for head contact'' in reducing the risk of concussion in 11–14 year old ice hockey players.

This is a mixed prospective and historical cohort study. Participants included 11–14 year old ice hockey players from Alberta and 11–12 year old players in Ontario (Canada). Independent variables included exposure to policy permitting body checking, exposure before or after head contact rule change, previous concussion, year of play, level of play, and player position. The primary outcomes included all diagnosed concussions.

Based on multivariate Poisson regression analyses (adjusted for cluster, exposure hours and other covariates), the concussion incidence rate ratio (IRR) associated with policy allowing body checking was 2.83 (95% CI; 1.09 – 7.31). The concussion IRR associated with head contact rule enforcement change in 11–12 year old players was 1.83 (95% CI; 1.18 – 2.86) and in 13–14 year old players was 2.74 (95% CI; 1.41 – 5.32).

The risk of concussion was 3-fold in 11–12 year old ice hockey players in leagues where body checking is permitted. The head contact rule enforcement policy change was not protective of concussion in 11–14 year old players. Referral bias related to a greater awareness of concussions may contribute to the greater risk post-head contact rule change despite consistent injury surveillance methodology. Policy disallowing body checking is effective in preventing concussion in youth ice hockey.

Key words
concussion, epidemiology, ice hockey, policy, prevention, youth

B4-21

GRAY MATTER ABNORMALITIES IN PEDIATRIC MILD TRAUMATIC BRAIN INJURY

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Pediatric mild traumatic brain injury (pmTBI) is the most prevalent neurological insult in children and is associated with both acute and chronic neuropsychiatric sequelae. However, little is known about underlying pathophysiology changes in gray matter diffusion and atrophy from a prospective stand-point. Fifteen semi-acute pmTBI patients and 15 well matched healthy controls (HC) were evaluated with a clinical and neuroimaging battery within 21 days of injury (mean = 14 days post), with a subset of 10 patients and 10 controls returning for a second visit at approximately 4 months post-injury. Clinical measures included tests of attention, processing speed, executive function, working memory, memory and self-reported post-concussive symptoms. Measures of diffusion (fractional anisotropy (FA)) and atrophy were also obtained for cortical and subcortical gray matter structures to characterize effects of injury as a function of time. Results indicated that patients exhibited decreased scores in the domains of attention and processing speed relative to controls during the semi-acute injury stage, in conjunction with increased anisotropic diffusion in the left superior temporal gyrus and right thalamus. Evidence of increased diffusion in these regions was also present at 4 months post injury, with performance on cognitive tests partially normalizing. In contrast, signs of cortical atrophy (Visit 2 cortical thickness – Visit 1 cortical thickness) in bilateral frontal areas and other left-hemisphere cortical areas only emerged at 4 months post-injury for patients relative to HC. Current results suggest potentially differential time-courses of recovery for neurobehavioral markers, anisotropic diffusion and atrophy following pmTBI. Importantly, these data suggest that relying on patient self-report or standard clinical assessments may underestimate the time for true injury recovery.

Key words
abnormalities, neuropsychiatric, pediatric, pmTBI, TBI

B4-22

SALIVARY BIOMARKERS OF STRESS REACTIVITY FOLLOWING PEDIATRIC TRAUMATIC BRAIN INJURY

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Very little is known about how traumatic brain injury (TBI) may impact stress systems. The objective of this study is to identify relations between biomarkers of stress reactivity, as measured by salivary cortisol and alpha-amylase, and psychological health outcomes following pediatric TBI.

Participants were drawn from a longitudinal prospective study composed of three groups of children ages 8–16: 1) mild, moderate, and severe TBI (n = 18) extracranial injury (n = 8), and healthy comparison children (n = 18). Cortisol and alpha amylase samples were collected at 5 time intervals before and after stress induction using the Trier Social Stress Test. The TSST is an established laboratory procedure involving oral speaking and mathematical calculation that typically produces time-linked elevation in both cortisol and alpha amylase. Psychological health outcomes included the Child Behavior Checklist Internalizing (anxiety, depression) and Externalizing (rule breaking, aggressive behavior) T-scores. Biomarkers and outcomes were assessed 6 months after injury.

Following assays of the salivary samples, cortisol and alpha amylase data were aggregated across time using area under the curve methodology. Spearman correlation coefficients examined the relations between each biomarker and psychological outcomes. For the total sample, cortisol levels were not significantly correlated with indices of psychological health. Alpha amylase was positively correlated with Externalizing ($r = .41$, $p < .01$) behavior problems. Within the TBI group, the Externalizing score was positively correlated with alpha amylase ($r = .69$, $p < .01$). Alpha amylase levels tended to be related to Internalizing scores for the total sample and the TBI subgroup.

Cortisol, a marker of hypothalamic-pituitary-adrenal axis function, did not correlate significantly with psychological health outcomes. Elevated levels of alpha amylase, a marker of adrenergic sympathetic nervous system stress reactivity, were significantly related to parent ratings of increased externalizing behavior problems. Following TBI, dysregulation of the autonomic nervous stress system may place children at risk for post-traumatic stress symptoms and contribute to dysregulation of emotions and behavior.

Key words
alpha amylase, cortisol, post-traumatic stress, psychological outcome, stress reactivity

B4-23

PEDIATRIC PATIENTS IN THE TRACK TBI TRIAL - TESTING COMMON DATA ELEMENTS IN CHILDREN

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In 2009, the NINDS and other agencies convened an effort to create a set of common data elements (CDE) for use in research in traumatic brain injury that would standardize definitions and data collection across centers, facilitate data sharing, and expand evidence for treatment evaluations. A parallel effort ensured that elements appropriate for children were included. TRACK TBI (Transforming Research and Acquiring Clinical Knowledge in TBI) is an 11-center, NIH-funded observational study which utilizes the CDE approach to enable comparative effectiveness research in TBI. We report here the development and use of the CDE platform for pediatric patients enrolled in TRACK TBI.

General and pediatric CDE consulting groups created recommendations for specific domains including demographics, clinical assessment, neuroimaging, biomarkers, and outcome measures; a second phase further refined elements deemed most important for specific patient groups or research areas. A 4-center pilot phase of TRACK TBI ensued which piloted the CDE's in adult patients. These elements were further expanded for TRACK TBI, an 11-center study involving 3000 TBI patients, so that pediatric patients could be readily

Specific pediatric considerations were necessary in all domains of data, including demographics (development, parent information, school setting), acute assessment (neurologic assessment tools for preverbal children), biomarkers and genetics (weight-based blood limits), imaging (rapid MRI protocols for unsedated young children), and validated, age-specific outcome measures. In all instances, choosing measures which could be compared both within and across age groups was prioritized. Consideration for age-specific consent/assent procedures, release of study-related results, recruitment incentives, and family concerns were addressed, in concert with participating centers' Institutional Review Boards.

Successful enrollment and followup of infants and older children into a large comprehensive database has been accomplished, and the CDE/TRACK TBI model may serve as a platform for other pediatric TBI clinical research studies.

Key words
biomarkers, clinical trial, comparative effectiveness, imaging, outcomes, pediatric

B4-24

THROMBIN AND PROTEASE-ACTIVATED RECEPTOR-1 ARE ACTIVATED IN INTRACTABLE EPILEPSY IN CHILDREN

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Disruption of the blood-brain barrier (BBB) has been implicated in the mechanisms of epileptogenesis following brain injury. Compromise of BBB integrity allows serum proteins including thrombin, access to the brain parenchyma. In hippocampal slice preparations, exposure to thrombin causes seizure-like activity via activation of the protease-activated receptor (PAR)-1. The role of thrombin in epileptogenesis in humans is not known.

We obtained resected brain tissues from 10 pediatric patients who underwent surgery for treatment of intractable epilepsy, and from age-matched postmortem controls. We used immunohistochemical methods to access; (a) integrity of the BBB (IgG; tight junction protein ZO-1); (b) expression of activated thrombin; and (c) PAR-1 receptor expression.

In the epileptic foci there was an increase in IgG immunoreactivity and a decrease in ZO-1 expression consistent with the disruption of BBB integrity. Expression of activated thrombin and PAR-1 was also increased in the brains of patients with intractable epilepsy, and was most prominent in white matter. Using double-labeling methods, we found that activated thrombin and PAR-1 is mainly expressed on astrocytes.

This is the first evidence of an increase in thrombin and activation of the thrombin receptor PAR-1 in human epilepsy. Taken together, the compromise of the BBB in chronic epilepsy, and expression of PAR-1 on astrocytes are preliminary evidence in human of a role for BBB injury and astrocyte-derived thrombin in the mechanisms of epilepsy, including post-traumatic seizures.

Key words
astrocytes, BBB, epilepsy, PAR-1, thrombin

B4-25

FACILITY-LEVEL CHARACTERISTICS AND PEDIATRIC IN-HOSPITAL MORTALITY FOLLOWING SEVERE TRAUMATIC BRAIN INJURY

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To enhance understanding of how facilities may improve pediatric traumatic brain injury (TBI) care and outcomes, we evaluated associations between facility characteristics and risk of 30-day in-hospital mortality among severe pediatric TBI patients in the National Trauma Data Bank from 2008 through 2012. Patients were included if they were <18 years of age at admission and stayed in the ICU for ≥2 days. Severe TBI was defined as a total Glasgow Coma Scale score on admission of <9, a head Abbreviated Injury Scale score of ≥3, and an International Classification of Diseases, Ninth Version code for TBI diagnosis (800.0-801.9, 803.0-804.9, 850.0-854.1, 950.1-950.3, 959.01, or 995.55). Patients were excluded if they were missing discharge disposition or had a total hospital stay of ≤2 days. Only Level I and II facilities were included. A total of 12,880 patient records in 441 facilities were analyzed. Multivariate Poisson regression models were used to calculate risk ratios (RR) for mortality while accounting for clustering by facility. Patient-level potential confounders included age, transfer status, hypotension and pulse at admission, mechanism of injury, severity of injury and ventilator use. Facility-level characteristics of interest included trauma center level, teaching status, region, number of beds, non-profit status and presence of pediatric trauma care. In the multivariate analysis, patients in the Midwest (RR = 1.48; 95% confidence interval (CI): 1.24, 1.75), West (RR = 1.30; 95% CI: 1.08, 1.57), and South (RR = 1.54; 95% CI: 1.32, 1.80) regions had a significantly higher risk of mortality (than those in the Northeast region (referent group). Other facility-level characteristics were not significantly associated with mortality. Significant regional variation in pediatric severe TBI mortality persists even after accounting for patient- and other facility-level characteristics.

Key words
epidemiology, facility chacracteristics, in-hospital mortality, severe TBI

B4-26

THE JUVENILE RAT BRAIN SHOWS INCREASED VULNERABILITY TO LOW IMPACT REPETITIVE INJURY OVER PROLONGED POSTTRAUMATIC INTERVALS

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Emerging evidence suggests that the juvenile brain may be more sensitive to TBI than the adult. Previously in adult rats, we have reported that the damaging cerebrovascular and axonal consequences of repetitive TBI were a function of both the injury intensity as well as the interval between repetitive injuries. The aim of the current study was to investigate if the threshold for repetitive injury as well as the intervals needed to evoke the damaging consequences of repetitive injury were reduced in juvenile rats. Further, in these studies we also assessed the neuroprotective effects of mild vs moderate hypothermia.

Seven and eight week juvenile rats were subjected to repetitive mTBI of varying severity employing different time intervals between the repetitive injuries followed by the use of either mild or moderate hypothermia. Impact-acceleration injury was used to elicit mTBI and vascular function was assessed through the use of cranial windows, followed by postmortem analysis of amyloid precursor protein immunoreactivity to assess the burden of axonal damage.

In rats of 8 weeks in age, a significantly reduced impact severity was needed to elicit cerebral vascular and axonal abnormalities compared to that previously reported in adults. Moreover in the 7 week rats, even further reductions in injury severity resulted in comparable changes. Further, in the juvenile rats, the window of risk between repetitive insults was significantly elongated compared to that seen in adults. Lastly, only the use of moderate hypothermia proved neuroprotective in the juvenile rats.

In conclusion, juvenile rats are more vulnerable to lower thresholds of injury for longer intervals between injuries compared to adult rats, with the caveat that moderate hypothermia can attenuate the damaging consequences of repetitive injury.

Supported by NIH Grant # NS077675

Key words
axonal injury, hypothermia, impact accelaration injury, juvenile rats, repetitive traumatic brain injury

B4-27

ACUTE MRS AND DTI FINDINGS AFTER MODERATE/SEVERE PEDIATRIC TBI

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We present findings on a prospective study comparing acute MRS and DTI findings in pediatric TBI patients to age-matched controls.

Pediatric patients, ages 4 to 18 years, were enrolled if they sustained moderate/severe TBI requiring (GCS < 13) OR (GCS > 13 if evidence of intracranial injury on initial computed tomography scan). Patients underwent 3T MRI with DTI and MRS in the acute period (6–17 days post TBI). TBI and control regional DTI metrics (FA, ADC, AD, RD) and MRS ratios (NAA/Cr, NAA/Cho, Cho/Cr) for the acute study were compared, according to severity of injury to age matched controls and correlated with neurologic (PCPCS) and neuropsychological outcomes at 12 months; general measures of memory utilizing the Children's Memory Scale (CMS: General Memory score), attention utilizing the Test of Everyday Attention for Children (TEA-CH: Teach G score), and the Wechsler Abbreviated Scale of Intelligence (WASI: Full Scale IQ).

We studied 58 children (43M); mean age 12.2 ± 3.5 yrs (5.2–17.9 yrs); initial GCS (Mild = 23; Moderate = 8; Severe = 27) and 54 controls; mean age 12.1 ± 3.3 yrs (5.5–17.4 yrs). Initial studies were obtained at 11.5 ± 3.4 days after injury. Follow-up studies were ob-

tained at 12.2 ± 3.5 months. NAA/Cr and NAA/Cho ratios were significantly reduced in severely injured patients compared to controls and mildly injured patients in all regions. Furthermore, NAA/Cr ratios were significantly different between all severity levels in frontal and temporal gray matter regions, and correlated with FSIQ, Memory Score and PCPCS from most regions. Only NAA/Cr from white matter regions correlated with the Attention score. Mean FA and AD were significantly reduced in severely injured compared to controls in basal ganglia, corpus callosum, and white matter regions and correlated with FSIQ and General Memory scores.

Early neuronal loss/dysfunction and axonal disruption correlate with long term intellectual and memory deficits. White matter injury may be more predictive of attention deficits. Support from NIH/NINDS:R01-NS054001

Key words
diffusion tensor imaging, magnetic resonance spectroscopy, neuropsychologic testing, pediatric, traumatic brain injury

B4-28

LONGITUDINAL TRACT-BASED ANALYSIS OF CALLOSAL DISRUPTION IN MODERATE/SEVERE PEDIATRIC TRAUMATIC BRAIN INJURY

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Brain imaging methods such as DTI (diffusion tensor imaging) are especially sensitive to white matter (WM) damage in TBI. However, analyses using tractography are complicated by damage and decreased FA (fractional anisotropy) characteristic of TBI, leading to premature tract endings. We examined pediatric moderate/severe TBI patients longitudinally in both the post-acute (2–4 months post-injury) and chronic phase (12 months post-injury). We used a newly-developed multi-atlas fiber tract clustering method to identify differences in callosal WM integrity. We assessed FA, RD (radial diffusivity), MD (mean), and AD (axial) along the corpus callosum (CC), in 6 segments. We had 67 post-acute participants: 31 TBI (mean age = 13.8 years, 7 F) and 36 control (mean age = 15.2 years, 16 F). Post-acutely, we found lower FA in TBI participants in the CC_frontal segment across a wide area of projections from the CC body and genu. We had 39 chronic participants: 19 TBI (mean age = 16.1 years, 5 F), and 20 control (mean age = 16.0 years, 7 F). In the CC_frontal, we found lower FA and higher RD and MD in TBI, particularly in the genu and bilateral projections of the CC body. In the CC_precentral, CC_postcentral, and CC_parietal segments, we found higher RD and MD in the CC body and bilateral projections. In the CC_temporal and CC_occipital, we found higher RD and MD in the splenium and lateral projections. These indicate that WM integrity differences between groups widen in the first year following TBI, due to both further decreases in integrity in some areas and smaller increases in integrity in the TBI group. This suggests continuing, progressive WM damage in the first year post-injury.

Key words
diffusion tensor imaging, fiber clustering, longitudinal, moderate/severe TBI, tractography

B4-29

ADOLESCENT REPEAT TRAUMATIC BRAIN INJURY CAUSES ACUTE CELL DEATH AND LONG-TERM INFLAMMATION IN THE ANTERIOR PITUITARY OF RATS

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Hypopituitarism is an increasingly common occurrence observed in adults and children after TBI. Despite the fact hormones play critical role in brain and physical development little attention has been paid to this area in adolescents. Previous studies have shown that a rat model of mild repeat concussion (RTBI) decreases growth hormone, insulin-like growth factor 1 and testosterone. Currently it is not yet understood whether the observed hormonal deficiencies are due to injury from the hypothalamus and/or the pituitary gland. Further, mechanisms responsible for chronic hormone dysfunction have not been delineated. It is hypothesized that due to location and anatomy of the pituitary gland RTBI will result in acute cell death and chronic activation of inflammatory processes. Male postnatal day 35 rats were given ether sham, 1 or 4 RTBI at 24 hr intervals. Western blots for α-II spectrin, GFAP and IL-1β were performed at 24 hrs, 72 hrs, 1 week and 1 month post-injury in both the hypothalamus and anterior pituitary (AP). No significant differences in protein levels were detected in the hypothalamus. In contrast, in the AP, there was a significant 86% decrease in α-II spectrin in RTBI animals at 24 hrs post-injury and significant 1062% and 400% increases in GFAP and IL-1β, respectively, 1 month post-injury. These results demonstrate that hypopituitarism following RTBI is due to mechanical injury to the AP and not the hypothalamus. In addition, combined with evidence of acute vascular damage in the AP following RTBI, this data suggest cell death within the AP is responsible for acute hormonal dysfunction while persistent inflammation may be responsible for chronic hormonal deficits. Further work is needed to determine both the mechanism of cell death within the AP and generation of chronic inflammation.

Marilyn & Austin Anderson, UCLA BIRC, NFL Charities

Key words
concussion, endocrine, hypothalamus, inflammation, pituitary, repeat traumatic brain injury

B4-30

HYPOTENSION PATTERNS AND VASOPRESSOR CHOICE AFTER SEVERE TRAUMATIC BRAIN INJURY ACROSS FIVE PEDIATRIC TRAUMA CENTERS

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We examined systemic hypotension (systolic blood pressure < 70 + 2*[age]) patterns and vasopressor use in 236 children ≤17 years with severe traumatic brain injury (TBI) during the first 72 hours after admission at different treatment locations [Pre-hospital (PH), Emergency Department (ED), Operating Room (OR) and Intensive

Care Unit (ICU)] across 5 pediatric trauma centers. Overall, 140 (59%) patients had at-least one hypotension episode. Hypotension occurred across treatment locations: OR (58/122;48%), ICU (101/236;43%), PH (44/210;21%) & ED (29/224;13%). Hypotension prevalence varied across centers for each location: PH (5–35%; $p = 0.01$), OR (16–74%; $p < 0.001$), and ICU (23–59%; $p = 0.001$). 65/236 (28%) had persistent (>1 location) hypotension, ranging from 13–50% across centers ($p < 0.001$). Hypotension treatment varied across centers: 1) 130/140 (93%; range 78–100%; $p = 0.002$) hypotensive children received fluids; 2) 75/140 (54%; range 38–72%; $p = 0.002$) received blood products and 3) 90/140 (64%; range 44–76%; $p = 0.12$) received vasopressors. 52/90 (58%) hypotensive patients received one and 38/90 (42%) received ≥2 vasopressors. Injury severity score (ISS) was greater only in those patients who received combination vs. single vasopressor therapy (mean ISS 34.2[SD15.4] vs. 30[SD11.3]; $p = 0.04$). The most commonly used single vasopressor was phenylephrine (22%), followed by epinephrine (13%), norepinephrine (12%), dopamine (8%) and vasopressin (2%). Vasopressor use varied by pediatric trauma center ($p < 0.001$). Overall, mortality rates ranged from (2–23%; $p = 0.02$). In conclusion, single episode, persistent, and refractory systemic hypotension are common after severe pediatric TBI and may be associated with variation in outcomes. Reducing variation in hypotension treatment, including vasopressor choice, may be important to improving TBI outcomes.

Key words
hypotension, outcomes, persistent, traumatic brain injury, vasopressors

B4-31

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME AFTER MILD TBI

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The incidence of recreation-related concussions in the United States is between 1.2–3.8 million per year. Post-concussive symptoms include headache, dizziness, cognitive issues, and mood disturbances. Symptoms typically resolve within 2 weeks, but may be prolonged, causing extended absences from school/work and withdrawal from normal activity. There are no standard treatments for concussion other than cognitive/physical rest. Autonomic dysfunction after TBI ranges from 8–33% of patients admitted to the ICU. While postural orthostatic tachycardia syndrome (POTS), a type of dysautonomia, has been described in case series in moderate/severe injuries, there is limited data after mild TBI. Dysfunction may manifest as disturbances in heart rate, blood pressure, and sweating/temperature. Symptoms may include dizziness, fatigue, headache, and decreased concentration. In this study, we aim to determine the prevalence of autonomic dysfunction after concussion, and characterize the relationship between POTS and post-concussive syndrome.

Data was prospectively collected from 52 individuals presenting to our sports concussion/mild TBI clinic. Orthostatic vital signs were obtained, and a threshold heart rate increase ≥30 signified identified patients with POTS. Symptoms were ascertained using the Graded Symptom Checklist portion of the Sport Concussion Assessment Tool (SCAT2).

18/52 (34%) of our patients had heart rate change consistent with POTS. The patients with POTS were less likely to have been injured by a sport-related mechanism (55.6% vs 73.5%), and more likely to be younger (average age 14.7 yrs vs 21.9 yrs).

A high proportion of symptomatic mTBI patients have concomitant objective evidence of autonomic dysfunction. These problems may potentially exacerbate headache, mood disturbances or other symptoms and may warrant a different treatment regimen. Careful risk factor assessment may identify those patients who suffer from POTS and manifest these post-concussive symptoms, enabling targeted treatments and decreasing recovery time. Comprehensive evaluation of symptomatic mTBI patients should include screening for autonomic dysfunction.

Support: UCLA BIRC, HD061504, Morris A. Hazan Friends of Semel Fellowship, NARSAD Young Investigator's Grant, Child Neurology Foundation/Winokur Family Foundation, Joseph Drown Foundation, Today's and Tomorrow's Children Fund

Key words
autonomic dysfunction, mild TBI, post-concussive syndrome

B5-01

PROGRESSION OF MYELIN PATHOLOGY IN TBI WITH TRAUMATIC AXONAL INJURY OF THE CORPUS CALLOSUM

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Traumatic brain injury (TBI) from impact-acceleration forces often results in post-concussive symptoms that persist into a chronic disease phase, even in patients diagnosed initially as mild TBI. To better understand the progression to chronic disease, we examined acute through chronic corpus callosum pathology in mice using a concussive TBI model of traumatic axonal injury (Sullivan et al., 2013 JNEN). TBI was produced in adult male *C57BL/6J* mice by impact onto the skull at bregma. Animals were perfused at multiple time points between 3 d-6 wks post-TBI and tissues were processed for either electron microscopy or immunohistochemistry. At all times post-TBI, degenerating axons were evident in the corpus callosum, particularly over the lateral ventricles. Degenerating axons were distributed among intact fibers – modeling the diffuse pattern of traumatic axonal injury in TBI. Axon diameters were reduced across the overall population of remaining axons. Demyelination may contribute to functional deficits and potentially leave denuded axons vulnerable to further damage. After TBI, demyelination of intact axons significantly increased at 3 d followed by remyelination evident at 1 wk. Furthermore, abnormal myelin figures were prevalent at all post-TBI times, yet rare after sham surgery. Myelin sheaths collapsed around degenerating axons and also formed long outfoldings, with or without an axon present. Due to this dispersed nature of demyelination and axon degeneration, oligodendrocytes may increase myelin synthesis to remyelinate intact axons or due to dysregulation in maintaining multiple sheaths among a cohort including intact and degenerating axons. Excessive myelin outfoldings may increase myelin debris, which can stimulate microglial activation. Immunohistochemistry demonstrated microglial activation and reactive astrogliosis that persisted 6 wks post-TBI. Myelin outfoldings were increased over 10-fold in comparison with cuprizone demyelination and remyelination. Further studies will be important to determine the contribution of this myelin pathology to persistent white matter neurodegeneration and neuroinflammation after TBI. Supported by the DoD in the Center for Neuroscience and Regenerative Medicine (CNRM).

Key words
corpus callosum, cuprizone, myelin, neuroinflammation

B5-02

DECREASED SEROTONIN TRANSPORTER EXPRESSION AFTER TRAUMATIC BRAIN INJURY IN A RAT CONTROLLED CORTICAL IMPACT MODEL

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Depression, higher brain dysfunction and aggression have been shown to occur after traumatic brain injury (TBI). Selective serotonin reuptake inhibitors (SSRIs) are effective in the treatment of such morbid states. Necropsy of the brain of patients showing mental depression revealed decreased density of serotonin transporter (5-HTT). We hypothesized that the serotonin transporter expression changes in the brain following TBI. We performed real-time polymerase chain reaction (PCR) analysis for mRNA and western blot analysis for protein to examine the time-dependent changes in the expression of 5-HTT in the brain during the first 14 days after TBI in a controlled cortical impact (CCI) model of rat brain. Compared to sham, decreased expressions of 5-HTT mRNA and protein were noted in the cortex on the side ipsilateral to the site of injury at 7 days after injury ($p < 0.05$). The findings indicated that TBI induced changes in 5-HTT expression in the ipsilateral cortex. The role of the serotonin transporter is to transport serotonin from the synaptic cleft into the synaptic region, enabling its use by the presynaptic neuron. Thus, the serotonin transporter regulates serotonin concentration in the synapse by recycling serotonin, and thereby affects the receiving neuron receptors. The decreased expression of 5-HTT after TBI could result in decreased serotonin neurotransmission in the brain.

Key words
controlled cortical impact, depression, serotonin, serotonin transporter

B5-03

LEUKEMIA INHIBITORY FACTOR DEFICIENT MICE HAVE AN INCREASED VULNERABILITY TO MILD PREDIATRIC TRAUMATIC BRAIN INJURY

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Cytokines and growth factors are key candidates for mediating the changes induced by damage to the brain as they can affect astrocyte proliferation, microglial activation and cell survival. Leukemia inhibitory factor (LIF), a member of the interleukin-6-type cytokine family, is rapidly induced after CNS injury and participates in all of these processes. However, whether LIF signaling is necessary for these injury responses has not been established. Therefore, to test the hypothesis that LIF is required for normal responses to pediatric traumatic brain damage, we compared the extent of damage to neocortical and subcortical white matter in LIF heterozygous and wild type (WT) mice. We performed a mild, closed-head controlled cortical impact (CCI) model at postnatal day 18 on WT and LIF heterozygous mice. In WT mice LIF transcripts increased ~15 fold 24 hours following mild TBI. This response was significantly reduced in LIF heterozygous mice. LIF haplodeficiency resulted in decreased astroglial activation (decreased GFAP expression) and a blunted microglial response (reduced Iba1 staining) after both mild and severe TBI in the neocortex and adjacent subcortical white matter. LIF deficient juvenile mice also exhibited greater apoptosis as demonstrated by increased in situ end labeling (ISEL) and increased neuronal cell death as shown by Fluorojade C staining in the neocortex and corpus callosum after mild TBI. These results indicate that LIF is necessary for the normal astrocytic and microglial responses to mechanical brain injury in immature mice. Supported by grant # CBIR13IRG017 from the NJ Commission on Brain Injury Research awarded to SWL.

Key words
leukemia inhibitory factor, pediatric mild TBI

B5-04

ACUTE ALTERATIONS IN GLUTAMATE NEUROTRANSMISSION AFTER CONCUSSIVE BRAIN INJURY

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Traumatic brain injury (TBI) is a major cause of morbidity and mortality, often leading to chronic neuropsychiatric symptoms. Glutamate neurotransmission requires neuron-astroglia-coupled regulation of synaptic and extrasynaptic glutamate levels. Glutamate mismanagement negatively impacts molecular correlates of cognition. We hypothesize that altered post-TBI intracellular signaling leads to dysregulated glutamate neurotransmission. TBI was initiated in parietal cortex using lateral fluid percussion (LFPI). The excitatory amino acid transporter 2 (EAAT2) was examined in synaptosomes isolated from ipsilateral LFPI cortex, sham-surgery, and naïve cohorts ($n = 5$) twenty-four hours post-LFPI using Western blot and 3H-labelled glutamate uptake. Serine/threonine kinase signaling was investigated in cortical and hippocampal homogenates using PamGene kinome arrays. Ingenuity Pathway Analysis (IPA) identified cellular processes corresponding to altered kinase activity. Twenty-four hours after LFPI, EAAT2 protein was decreased in cortical homogenate in LFPI, but not synaptosomes. Synaptosomal glutamate uptake decreased after LFPI. Twenty-seven kinome array substrates in cortex, and nineteen in hippocampus were differentially phoshorylated between LFPI and controls (fold change $+/-1.15$). Among these, were components of multiple mitogen-activated protein kinase (MAPK) cascades which are instrumental in mediating both inflammation and glutamate regulation. In cortex, IPA identified cell death and survival, organismal survival, and glucocorticoid signaling as the most probable cellular functions, physiological systems and signaling pathways affected by the alterations in kinase activity. In hippocampus, LFPI impacted cellular assembly and organization, nervous system development and function, and Protein Kinase A signaling. These data identify molecular cascades and subsequent glutamate dysregulation as a potential mechanism for cognitive and behavioral impairment after TBI. These findings highlight the importance of determining the long-term status of the EAAT2 system and synaptic glutamate management after TBI.

Key words
excitatory amino acid transporter, extrasynaptic, glutamamte, lateral fluid percussion, localization

B5-05

BLAST EXPOSURE PHOSPHORYLATES TAU PREFERENTIALLY AT SERINE396, WHICH CAN TRIGGER ALZHEIMER'S-LIKE PATHOLOGY

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Blast-induced traumatic brain injury (TBI) is one of the major disabilities in service members returning from recent military operations. Blast-induced TBI is associated with acute and chronic neuropathological and neurobehavioral deficits. Epidemiological studies indicate that brains of 30% of victims who die acutely following TBI have Aβ plaques, a pathological feature of Alzheimer's disease (AD), which suggests that TBI may predispose to AD, although to date this notion remains somewhat speculative. *Tau* protein, phosphorylated at serine396 (S396), is rich in paired helical filaments which form neurofibrillary tangles (NFTs) observed in the brains of patients with AD. The number of NFTs is tightly linked to the degree of dementia, indicating that the formation of NFTs may underlie and contribute to neuronal dysfunction. Preliminary studies carried out in our laboratory using shock tube models of single and repeated blast-induced TBI in rats indicate that phosphorylation of *Tau* protein occurs preferentially at S396. S396 phosphorylation of *Tau* varied in different regions of the brain and the degree of phosphorylation increased with number of blast exposures. Increased S396 phosphorylation occurred acutely after blast exposures and chronically returned towards normal levels which at this stage did not positively correlate with the accumulation of amyloid precursor protein (APP) that occurred chronically. These results indicate that acute *Tau* protein phosphorylation at S396 and chronic accumulation of APP in the brain after blast exposure may predispose to Alzheimer's-like disease.

Key words
Alzheimer's disease, Alzheimer's-like pathology, blast exposure, traumatic brain injury

B5-06

PROLONGED INCREASES IN 22 KDA TAU FRAGMENT FOLLOWING PENETRATING TBI

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Tau is a protein involved in stabilizing microtubules in axons. Here we determine whether there are changes in levels of tau or tau fragments within the acute and subacute time frames following penetrating ballistic-like brain injury (PBBI). PBBI involves the rapid inflation/deflation of a custom probe causing a temporary cavity that in this case equaled 10% of total brain volume. Brain tissue was collected ipsilaterally within the injury tract at 4 and 24 hr, 3 and 7 days post-injury ($n = 8 - 10$). Tau levels and tau fragmentation was analyzed by immunoblot and normalized to beta-actin levels. Tau levels during PBBI are compared to probe only (no temporary cavity) and sham controls. Full length tau levels (55 kDa) were not altered 4 hr post-injury. By 24 hr post-injury, probe and PBBI tau levels were decreased 39% and 42%, respectively. At 3 days post-injury 73% and 89%, respectively; and at 7 days post-injury 87% and 96%, respectively. A 40 kDa fragment showed similar temporal decreases: 35% (probe, $p < 0.05$) and 45% (PBBI, $p < 0.05$) at 24 hr, 78% (probe, $p < 0.001$) and 94% (PBBI, $p < 0.001$) at 3 days, and 80% (probe, $p < 0.001$) and 93% (PBBI, $p < 0.001$) at 7 days. In contrast, a 22 kDa tau fragment, known for its involvement in tauopathies, including Alzheimer's disease, increased dramatically following injury: 544% (probe, $p < 0.01$) and 1541% (PBBI, $p < 0.001$) at 4 hr and 893% (probe, $p < 0.05$) and 2367% (PBBI, $p < 0.01$) at 24 hr. At 3 and 7 days post-injury PBBI levels again were significantly increased 1541% and 2424%, respectively Changes in tau levels and tau fragment levels are clearly influenced by injury severity (probe vs PBBI). Ongoing studies will determine if the dramatic increases in the 22 kDa tau fragment can be detected at more chronic time-points (i.e. month post-PBBI). Collectively, these early changes in tau fragmentation may be useful as prognostic indicators of neurodegenerative tauopathies utilizing *in vivo* neuroimaging such at positron emission tomography, and as early markers of therapeutic efficacy.

Key words
neurodegeneration, PBBI, severe TBI, tau

C1-01

MATRIX METALLOPROTEINASES AS A THERAPEUTIC TARGET FOR SUPPORTING UROLOGIC RECOVERY IN A MURINE MODEL OF SPINAL CORD INJURY

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Matrix-metalloproteinases (MMPs), and in particular MMP-9, are upregulated in the acutely injured spinal cord and their transient, short-term blockade with a general MMP-inhibitor (MMPI), beginning 3 hours post-injury and for the next 3 days, results in long-term locomotor recovery and greater sparing of white matter. As sparing of white matter may at least in part reflect preservation of long descending fiber tracts including those involved in the control of bladder function, we hypothesized that acute blockade of MMPs would lead to improved urological function. Testing this hypothesis, we conducted a randomized, blinded pre-clinical study, in which adult male C57Bl/6 mice were subjected to a moderate contusion injury ($n = 23$) at the level T9 and were treated with either an MMPI or vehicle. As neutrophils are a major source of MMP-9, treatments were initiated 8 hours after injury, a time corresponding to prominent neutrophilia in the humoral compartment. Neurological and urological recovery was assessed using the Basso Mouse Scale and conscious cystometry, over a period of 5 weeks and at 6 weeks post-injury, respectively. Stereology was used to determine lesion volume and white matter sparing. As bladder dysfunction is associated with aberrant wound healing resulting in increased bladder wall thickness, this parameter was measured at the time of euthanasia. In the MMPI-treated group there were significant long-term improvements in locomotor function, sparing of white matter and voiding function, as evidenced by decreased post-void residual urine and enhanced voiding efficacy. Moreover, there were fewer uninhibited bladder contractions per voiding cycle, an indicator of decreased bladder over-activity, and detrusor wall thickness was significantly less compared to vehicle controls. In summary, delayed treatment with an MMPI improved both locomotor and bladder function. These

findings, together with an extended therapeutic window, offer promise for translation to the clinical setting.

Funding: DOD-SC100140

Key words
neurogenic bladder dysfunction, spinal cord injury

C1-02

GENE EXPRESSION CHANGES IN RESPONSE TO SELENIUM DIET IN SPINAL CORD INJURED RATS

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Certain groups at high risk for spinal cord injury (SCI) groups may benefit from a prophylactic supplement, such as dietary selenium, that would intervene in the secondary neurodegenerative cascade immediately following trauma. The high demand for selenium within the CNS, as well as the synthesis of selenoproteins by neurons and astrocytes suggests a critical role of selenium within the brain and spinal cord. Selenium was supplemented in the diets of female Sprague-Dawley rats prior to receiving a moderate (150 kdyn) contusive spinal cord injury or sham laminectomy. Twenty-four hours following injury, 7 mm of spinal cord directly surrounding the injury epicenter was collected from animals on both diets, sham and injured. RNA was isolated from these tissues, converted to cDNA, and utilizing the Affymetrix genome array platform, hybridized to rat microarray genome chips with probe sets representing 31,097 genes. Raw signal intensities from Affymetrix scanner were converted to gene expression summary values using RMAExpress. Genes underwent a rigorous selection process, which resulted in a 14,907 filtered gene list. These genes were subjected to a 2-way ANOVA, and filtered further based upon a Bonferonni correction for 3 tests using genes that met the criteria of $p < 0.017$. The resulting list was sorted into templates based on their expression patterns in the four treatment groups. A total of 4301 and 4812 genes were consistently down-regulated and up-regulated, respectively, across diet groups in response to the injury. Of particular interest, a template that isolated 78 genes specifically down-regulated in the control injured group showed these phenotypes rescued in selenium injured animals, including genes associated with transcriptional regulation and cell cycle arrest. Additionally, another template showed 111 genes up-regulated in selenium injured animals when compared to control injured animals. These genes include pathways associated with DNA repair, mitochondrial function, and protein turnover. These tools will help us to understand mechanisms of selenium in the central nervous system in response to injury.

Key words
dietary, gene expression, selenium, spinal cord injury

C1-03

EFFECT OF A GNRH AGONIST ON LOCOMOTION, GAIT AND SPINAL CORD MORPHOLOGY IN RATS WITH SPINAL CORD INJURY

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It has been reported that Gonadotropin-releasing Hormone (GnRH) has neurotrophic effects, improves locomotor activity and urinary function of rats with spinal cord injury (SCI). Our aim was to determine whether administration of a GnRH agonist (GnRH-A) improves locomotion, gait and spinal cord morphology in rats with SCI.

Ovariectomized adult female Wistar rats were divided in five groups. Sham SCI (Sham), control SCI treated with saline solution (SS), SCI treated with GnRH-A at dose 1.2 μg/kg (GnRH-A 1), 5 μg/kg (GnRH-A 2) and 10 μg/kg (GnRH-A 3). The lesion was performed using a compression model. A Fogarty catheter was introduced at T-12 level and the catheter balloon was insufflated to 20 μl during five minutes. All animals were sacrificed 6 weeks later. One day after SCI, GnRH-A was administrated three consecutive days, and followed by an administration every 4 days during 6 weeks. One day after SCI, all groups were evaluated weekly according to the BBB scale, gait (path time, distance and speed stride) and spinal cord morphology (white and gray matter spared area) by histochemistry.

We found that, at the sixth week, GnRH-A treatment improves the movement, being a 40%, 35% and 41% of recovery in GnRH-A 1,2 and 3 respectively, while SS group was 7% only in the BBB scale. In gait analysis, GnRH-A groups decreased the time, increased both, distance and speed of the path compared to SS group. According to the area of spared tissue, gray and white matter was higher in treated groups compared to SS group, but only GnRH-A 2 had a significant difference. In conclusion, GnRH-A treatment improves locomotion, gait, and the morphology of the spinal cord in rats with SCI, providing a potential alternative treatment for spinal cord injuries.

Key words
gait, GnRH agonist, locomotion, spinal cord

C1-04

MODULATION OF INFLAMMATORY RESPONSES BY SOLUBLE TNF RECEPTOR IN A RAT MODEL OF CERVICAL SPINAL CORD INJURY (SCI)

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Initial mechanical damage to the spinal cord induces acute inflammatory responses that contribute to secondary injury and cell death, thus impairing functional recovery. Following SCI, TNFα initiates downstream inflammatory cascades and is a key mediator of excitotoxic injury by increasing synaptic calcium-permeable AMPA receptor expression. Previous work in our lab has shown intrathecal delivery of sTNFR1 can significantly improve behavioral outcome and reduce microglial activation at the injury site during 6 week evaluation. The goal of the current study is to investigate the mechanisms through which intrathecal sTNFR1 mediates inflammatory responses and helps to improve function following SCI.

Long-Evans female rats ($n = 52$) received intrathecal delivery of 350 ng sTNFR1 90 minutes following unilateral C5 contusion injury (75 kdyne) or C5 laminectomy without injury. Animals were sacrificed at 3 h, 24 h or 7 d after injury. In two groups, spinal cord, serum and spleen samples were harvested and analyzed for inflammatory markers by Luminex multiplex assay or quantitative PCR. In other groups, animals were used for spinal cord histological assessment and flow cytometric analysis of peripheral leukocytes. Early after SCI,

inflammatory cytokines are significantly up-regulated in both spinal cord and peripheral tissues (serum and spleen). Intrathecal sTNFR1 reduces spinal cord TNFα levels and modulates key anti-inflammatory mediators in the serum and spleen. Histology reveals reduced numbers of ED-1 positive cells at the injury site after sTNFR1 at both 24 h and 7d post-SCI. Further, by flow cytometry, we find decreased CD11b ^{high} monocytes in peripheral blood following sTNFR1 treatment.

Our data demonstrate both local and systemic inflammatory responses are activated following SCI and improved functional outcome with TNFα inhibition is associated with mitigated local inflammatory responses in the spinal cord. Intrathecal sTNFR1 also results in reduced expression of peripheral inflammatory markers and mediates a reduction in the circulating pool of inflammatory monocytes.

Key words
immune response, macrophage, neuroinflammation, soluble TNF receptor, tumor necrosis factor alpha

C1-05

KALLIKREIN CASCADES IN TRAUMATIC SPINAL CORD INJURY: DIFFERENTIAL ROLES IN AXONOPATHY AND NEURON DEGENERATION

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The inventory of proteases involved in traumatic spinal cord injury (SCI) is long and growing and includes members of the matrix metalloprotease family, cysteine proteases and serine proteases of the thrombolytic, fibrinolytic and tissue kallikrein (KLK) families. The current effort focused on defining the involvement of kallikreins in traumatic SCI, with an emphasis on those expressed at significant levels in the CNS or which are linked to pathology in other neuropathologies. Kallikreins comprise a family of 15 secreted serine proteases that form the largest contiguous cluster of serine proteases in the human genome. To illuminate their contributions to the pathophysiology of SCI, we evaluated alterations in the immunohistochemical appearance of six kallikreins, KLK1, KLK5, KLK6, KLK7, KLK8 and KLK9 in post-mortem human SCI cases from acute through chronic time points, quantified changes in the expression of each at an RNA level in a murine SCI model, and assessed their neurotoxic properties toward murine cortical neurons *in vitro*. Temporally and spatially distinct changes in kallikrein expression were observed with partially overlapping patterns between human and murine SCI, including peak elevations during the acute and subacute periods. In the SCI model, alterations in kallikrein expression paralleled peak transcriptional elevations in pro-inflammatory cytokines IL-6, TNF-α and IL-1β, in elevated levels of expression of GFAP, and in transcriptional reductions in RNA encoding for myelin genes. In both human and murine SCI, KLK9 showed the most significant changes and remained elevated chronically. In cases of human SCI, each kallikrein was also associated with swollen axons and retraction bulbs. Importantly, a subset of kallikreins, KLK1, KLK5, KLK6, KLK7 and KLK9 were shown to be neurotoxic toward primary neurons *in vitro*. The injury-related changes in kallikrein expression documented, taken with their differential neurotoxic effects, indicate that elevated levels of a large subset of kallikreins are positioned to contribute to pathogenesis secondary to SCI and therefore may represent new therapeutic targets.

Key words
human, protease, spinal cord injury

C1-06

MODULATION OF MATRIX METALLOPROTEINASES AFTER SPINAL CORD INJURY IMPROVES FUNCTIONAL RECOVERY OF RATS

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Spinal cord injury (SCI) results in a multitude of changes affecting several different cell types, leading to a complex pathological picture. Secretion of matrix metalloproteinases (MMPs) into the injured spinal cord results in activation of several signaling pathways which contributes to secondary damage. Based on our published results, we hypothesized that intraspinal administration of MMPs would aid in the alleviation of neuropathic pain, help prevent further secondary damage, and activate signaling pathways which help in tissue restoration and functional recovery. We used contusive injury in the rats using NYU impactor and observed that infiltration of microglia to the site of injury started as early as 1d post-SCI. We observed that maximum infiltration of microglia took place by 7d post-SCI at the injury epicenter; and therefore we decided to administer MMPs on 8th day after SCI. On the 8th day after SCI, MMP2 overexpression plasmid/shMMP9/shMMP12 dissolved in sterile PBS was injected intraspinally at a distance of 5mm away from the site of injury on each side (rostral and caudal). Our results indicated that intraspinal administration of MMP2 inhibited glial scar formation and expression of neurocan. Treatment either with shMMP9 or with both shMMP9 and shMMP12 seemed to highly upregulate Osteopontin in the injury epicenter, suggesting that knockdown of both MMP9 and MMP12 helped the extracellular matrix of injured portion of spinal cord to undergo reparative processes. Intraspinal administration of MMP2 showed greater improvement of hind limbs compared to injured rats. On the other hand, the shMMP-12 group rats showed considerable improvement in the functional scores compared to shMMP9 group rats. However, we observed an additive effect when both shMMP9 and shMMP12 were given together. These results suggest that treatment with either overexpression of MMP2 or knockdown of MMP9/MMP12 shows promising results, which can be exploited for future translation therapy after SCI.

Key words
glial scar, matrix metalloproteinases, neuropathic pain, osteopontin

C1-07

PHARMACOLOGICALLY TARGETING L-SELECTIN IMPROVES OUTCOMES FOLLOWING SPINAL CORD INJURY

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Demyelination is a key determinant of neurological recovery following spinal cord injury (SCI). There is no widely accepted therapeutic for SCI or effective interventions for secondary demyelination. While leukocyte depletion studies have shown attenuation of early demyelination following SCI, the underlying mechanisms mediating pathogenicity between leukocytes and myelin have remained elusive. We have found reduced degradation of myelin basic protein, long-term improved neurologic recovery, and increased white matter sparing in L-selectin knockout (KO) mice following SCI. These data suggest that L-selectin, a receptor expressed on all leukocytes, could be a novel target for therapeutic intervention for SCI. To test this hypothesis, we conducted blin-

ded, randomized preclinical trials to investigate the potential for diclofenamic acid (DFA), a potent L-selectin sheddase approved by the FDA for the treatment of inflammatory disorders in humans, as a therapeutic following SCI. We first utilized enzyme-linked immunosorbent assays and flow cytometry to quantify L-selectin sheddase activity post-SCI in blood and cord after intraperitoneal administration of DFA (at 1, 5, 10, 20, 40, or 60 mg/kg) and determined the minimally effective dose to be 40 mg/kg. Next, 40 mg/kg DFA or vehicle was administered to mice immediately following either a moderate or severe contusion SCI (n = 15/group). Locomotor recovery, based upon the Basso Mouse Scale, was significantly improved with DFA treatment relative to vehicle controls in both injury severities. Critically, the percentage of moderately injured mice frequently/consistently stepping improved from 45% (vehicle) to 92% (DFA) and of severely injured mice stepping from 8% (vehicle) to 70% (DFA). Finally, efficacy of 40 mg/kg DFA was investigated when treatment was delayed 3 hours post injury (n = 15/group). DFA treatment again showed significant locomotor recovery in severely injured mice with the percentage of mice stepping improving from 18% (vehicle) to 62% (DFA). Together, these encouraging data support the repurposing of FDA-approved DFA for the treatment of SCI.

Key words
diclofenamic acid, inflammation, L-selectin, secondary demyelination, spinal cord injury

C1-08

ROLE OF CPLA2 IN THE PATHOGENESIS OF SPINAL CORD INJURY

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Several lines of evidence suggest that phospholipase A_2 (PLA_2) may play a key role in mediating secondary spinal cord injury (SCI). PLA_2 are a diverse family of lipolytic enzymes which hydrolyze phospholipids to produce free fatty acids and lysophospholipids. Cytosolic PLA_2 ($cPLA_2$) is one of the most important PLA_2 isozymes. However, the role of $cPLA_2$ in the pathogenesis of SCI has not yet been fully understood, and is even controversial. In this study, we investigated whether $cPLA_2$ plays a role in the pathogenesis of SCI using multiple approaches including cellular, molecular, pharmacological, genetic, and behavior assessments. The results showed that SCI significantly induced $cPLA_2$ expression and activation. Activated $cPLA_2$ was localized mainly in neurons and oligodendrocytes. Notably, SCI-induced $cPLA_2$ activation was mediated, at least in part, by the ERK signaling pathway. *In vitro* experiments showed that activation of $cPLA_2$ by ceramide-1-phosphate, a direct $cPLA_2$ activator, or A23187, an indirect $cPLA_2$ activator, induced spinal neuronal death, which was substantially reversed by AACOCF3, a $cPLA_2$ inhibitor. TUNEL staining and Western blot further revealed that $cPLA_2$ activation induced neuronal death through apoptosis. Remarkably, blocking $cPLA_2$ pharmacologically with AACOCF3 reduced $cPLA_2$ activity, membrane injury, inflammation, cell death, and tissue damage, as well as improved behavioral recovery in C57BL/6 mice after SCI. A important finding of the present study is that genetic deletion of $cPLA_2$ resulted in neuroprotection and behavioral recovery following SCI. Genetic deletion of $cPLA_2$ also inhibited the expression of active caspase-3 after SCI, suggesting that $cPLA_2$ activation mediates neural apoptosis. These findings collectively suggest that $cPLA_2$ may play a key role in the pathogenesis of SCI, and this molecule could be an attractive therapeutic target for ameliorating secondary tissue damage and promoting recovery of function after SCI.

Key words
behavioral function, cytosolic phospholipase A2, inflammation, neuronal death, spinal cord injury

C1-09

AC105 INCREASES DELIVERY OF EXTRACELLULAR MAGNESIUM TO INJURED SPINAL CORD TISSUE IN RATS

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Magnesium (Mg^{++}) plays an essential role in maintenance of numerous cellular functions and has beneficial effects in rat models of spinal cord injury (SCI). Studies have shown that the neuroprotective effects of supplemental Mg^{++} following SCI were achieved only with extremely high doses of $MgSO_4$. It was recently reported that infusion of $MgCl_2$ in a polyethylene glycol (PEG, MW 3350 g/mol) formulation (named AC105 and currently under clinical development for SCI by Acorda Therapeutics Inc.) was neuroprotective at a relatively low dose of Mg^{++}. The aim of this study was to compare the extracellular Mg^{++} levels in SCI rats after treatment with AC105, $MgSO_4$ or saline. SCI was induced in isoflurane-anesthetized rats (female Long Evans, 200–250 g) by temporary compression of the spinal cord following laminectomy at the T9/T10 vertebral level. Two microdialysis probes were inserted transversely through the spinal cord, one positioned at the center of the compression site and the other 1 mm rostral to the compression site (peri-lesion zone). Dialysates were collected every 15 minutes for 4 hours following SCI. AC105 ($MgCl_2$, 192 μmol/kg, n = 15), $MgSO_4$ (192 μmol/kg, n = 15), or saline (5 mL/kg, n = 15) was intravenously infused over 30 minutes beginning 2 hours after SCI. Dialysate samples were analyzed for Mg^{++} and K^+ concentrations using inductively coupled plasma optical emission spectrometry. We find that AC105 treatment produced a sustained, significant increase in extracellular Mg^{++} both within the compression zone ($\sim$1.5- to 2-fold, $p < 0.01$, two way ANOVA followed by Bonferroni test) and the adjacent rostral zone ($\sim$1.3- to 1.5-fold, $p < 0.01$) following SCI, relative to saline, while $MgSO_4$ produced a slight but not statistically significant increase in the respective dialyzed zones after SCI. No statistically significant change in extracellular K^+ concentration was observed between pre- and post-treatment in all three groups. These results indicate that AC105, compared to equimolar $MgSO_4$, enhances delivery of extracellular Mg^{++} to spinal cord tissue following traumatic injury.

Key words
magnesium, microdialysis, polyethylene glycol, rats, spinal cord injury

C1-10

CONDITIONAL SILENCING OF ADULT RAT SPINAL LOCOMOTOR CIRCUITRY INDUCES HOPPING

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Identifying the functional role of spared neural pathways post-spinal cord injury can help design targeted rehabilitation strategies to

enhance recovery. Methods to functionally dissect locomotor circuitry primarily consist of non-specific spinal lesions or a limited number of neuron-specific, fate-mapped transgenic strains. A conditional two viral vector system was recently developed, allowing specific neuronal pathways to be functionally silenced based solely on their anatomy. Targeted neurons are silenced *in vivo* through reversible expression of enhanced tetanus neurotoxin (eTeNT) that proteolytically cleaves vesicle-associated membrane protein 2, which is essential for synaptic vesicle exocytosis. Here, we conditionally silenced L2 interneurons with descending projections to L5. Those neurons were double-infected by bilateral injections of HiRet-TRE-EGFP.eTeNT at L5 and the tetracycline-responsive AAV2-CMV-rtTAV16 at L2. Doxycycline (DOX, 15 mg/ml) was given *ad libitum* to induce eTeNT expression. Behavioral, kinematic, gait, and electrophysiological assessments were performed pre-injections, before DOX-induced neurotransmission silencing, during DOX treatment (DOX^{ON}), and post-DOX. DOX^{ON} was repeated one month later to assess reproducibility. Silencing descending L2 interneurons induced a hop-like phenotype in the hindlimbs. Hopping was quantified by a significant increase in average hip excursion and changes to locomotor-related measures, including hindlimb swing, stance, and stride during volitional and treadmill-based stepping. L2-L5 interneuron silencing switched the step sequence pattern from alternate to cruciate wherein forelimb stepping precedes hindlimb, as opposed to alternation. These DOX^{ON} functional changes were replicated one month after DOX washout. Current studies focus on long ascending propriospinal neurons (LAPNs), a neural pathway thought to functionally interconnect hind- and forelimb central pattern generators. Bilateral injections of eTeNT at C6 and rtTAV16 at L2 doubly-infected LAPNs. DOX treatment induced a symmetrical hop-like gait involving both fore- and hindlimbs during volitional locomotion. Ongoing behavioral, kinematic, gait, and electrophysiological analyses are being performed to quantitatively describe this locomotor behavior. This approach enables delineation of the functional contribution of propriospinal pathways in normal locomotor function, after spinal cord injury, and importantly after targeted rehabilitative therapy.

Support: GM103507,KSCHIRT 13–14.

Key words
locomotion, molecular biology, motor pathways, spinal circuitry

C1-11

INDUCED HYPERTENSION DOES NOT IMPROVE OUTCOMES IN PENETRATING SPINAL CORD INJURY

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Many trauma centers treat traumatic spinal cord injured-patients with MAP goals greater than 85–90 mm Hg. However, there is a lack of high grade evidence to support this practice or to identify the best target blood pressure. There is even less evidence to weigh towards specific BP goals for penetrating spinal cord injuries (SCI). We studied our own experience in using pressors to maintain a MAP goal greater than 85–90 in patients with penetrating SCI.

We retrospectively reviewed penetrating spinal cord injuries treated at a single academic medical center (San Francisco General Hospital) from 2005–2011. For inclusion, we required an ASIA grade on admission and discharge. Exclusion criteria included inadequate clinical documentation and non-penetrating injury.

Nineteen cases met inclusion criteria. 1 case was excluded for inadequate documentation of the ASIA grade. In the remaining 19 cases, mean age was 40.1 (range 18–93). Mean injury severity score was 28.8 (range 9–75). Mean hospital stay was 20.6 days (range 1–151). Six patients had concomitant TBI. Initial American Spinal Injury Association (ASIA) grade was A for 13 patients, C for 1 patient, and D for 5 patients. 18 patients received pressors in order to maintain MAP goals. 17 ASIA grades were unchanged at the time of discharge. Two patients improved: one from ASIA A to B and the second from C to D. One patient worsened from ASIA C to B.

There was no obvious benefit to blood pressure augmentation in a retrospective, single-center study of penetrating, traumatic SCI. Two patients improved by one ASIA grade and another worsened by one ASIA grades. Further study is needed to assess whether there is a role for blood pressure augmentation in patients with penetrating SCI.

Key words
mean arterial pressure (MAP), penetrating spinal cord injury

C2-01

COMBINATION THERAPY WITH PROGESTERONE AND VITAMIN D PROTECTS THE NEUROVASCULAR UNIT AFTER TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) is a highly complicated disease which comprises a primary insult and a progressive secondary cascade of inflammatory and immune responses resulting in neurological deficits. Previous studies have shown that progesterone and vitamin D hormone (VDH) can individually reduce inflammatory responses induced by TBI and this effect might be modulated through TLR-mediated pathways. In the present study, we investigated the effect of progesterone (i.p., 16 mg/kg body weight) combined with VDH (1ug/kg body weight) on maintaining neurovascular unit integrity by helping to control acute neuroinflammation post-TBI. We observed that the expression of TLR4 but not TLR2/6 increased significantly at 24 h after TBI insult. Immunostaining showed that increased expression of TLR4 was labeled extensively on neurons, endothelial cells and microglia. The combination treatment, but not either individual treatment, significantly reduced TLR2/4 expression at 24 h post-TBI. Neither the combination treatment nor individual treatment affected TLR6 expression at 24 h post-TBI. Progesterone and VDH as well as the combination treatments inhibited the expression of pro-inflammatory factor IL-1β compared to vehicle alone. However, only the combination treatment was statistically significant in inhibiting the expression of TNFα compared to vehicle. Importantly, the combination treatment reduced neuron loss and inhibited astrocyte activation significantly compared with the two individual drugs evaluated by Western blot. Immunostaining for CD68, CD31, and claudin-5 showed that combination treatment inhibited the activation of microglia and enhanced blood-brain barrier integrity significantly compared to progesterone or VDH given separately. In conclusion, our results suggest that combination therapy results in better protection of the neurovascular unit after TBI than progesterone or VDH given individually. The combination therapy helps to modulate TLR-mediated acute neuroinflammation.

Key words
combination therapy, progesterone, secondary injury, toll-like receptor

C2-02

COMBINING ENRICHED ENVIRONMENT AND INDUCED PLURIPOTENT STEM CELL THERAPY RESTORES FUNCTION FOLLOWING TRAUMATIC BRAIN INJURY

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Despite advances towards potential clinically viable therapies there has been only limited success in improving functional recovery following traumatic brain injury (TBI). Exposure to an enriched environment (EE) improves memory, learning, and motor skill development. Induced pluripotent stem cells (iPSCs) have been shown to survive transplantation and influence functional recovery. The current study evaluated EE/iPSC as a polytherapy for remediating deficits following medial frontal cortex (mFC) controlled cortical impact (CCI) injury. Sixty adult male rats received a midline mFC CCI or sham injury. Following surgery, rats were randomly placed in either EE or standard environment (SE). Seven days later injured rats received bilateral transplantation of either 100,000 iPSCs or vehicle. Behavioral measures included the Open-field, vermicelli handling (VHT), Morris water maze (MWM), and Rotarod (RR) tasks. Brains were perfused, extracted, and embedded in paraffin. The brain tissue was sliced into 30 μm thick sections and labeled with hematoxlyn and eosin; additionally, 250 μm thick sections were cleared using SeeDB and labeled with GFAP, MAP2, and NeuN. Open-field data revealed that injured rats had initially lower activity levels when compared to shams. However, the long lasting effects of combined therapies resulted in activity patterns typical of enriched shams. On the VHT, rats that received EE/iPSC polytherapy performed better than HBSS-treated rats. Rats exposed to EE or iPSCs performed equivalently to Sham/EE rats on the MWM. Proficiency on the RR was consistently better in EE housed groups as compared to their SE counterparts. Confocal microscopy confirmed that iPSCs survived, migrated away from the transplantation site, and expressed neural phenotypic characteristics. Overall, rats that received either EE or iPSC therapy improved on cognitive and motor tasks, however, full cognitive restoration was seen only with the EE/iPSC polytherapeutic approach. These data suggest that EE/iPSC therapy should be explored as a potential, clinically relevant, polytherapy for the treatment of TBI.

Key words
enriched environment, induced pluripotent stem cell, iPSC, polytherapy, SeeDB, traumatic brain injury

C2-03

TRAUMATIC BRAIN INJURY REDUCES VASCULAR REACTIVITY IN AGING RAT MIDDLE CEREBRAL ARTERIES

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Age is a consistent predictor of poor outcome following traumatic brain injury (TBI) (Mosenthal,et al., 2002; Susman, et al., 2002). The causes for the adverse effects of age on brain injury remain obscure. In experimental animals and patients, TBI reduces cerebral vascular compensatory responses to changes in arterial blood pressure (DeWitt & Prough, 2003). Aged rats subjected to weight drop TBI exhibited reduced cerebral-blood-flow (CBF) and significantly reduced hyperemia following posttraumatic-hypoperfusion (Biagas, et al., 1996). Here we test the hypothesis that age reduces the post-traumatic vascular reactivity of the middle cerebral artery (MCA). Old (22–24 months) and young (3–4 months) male rats (n = 16/group) were anesthetized with isoflurane, intubated, and mechanically ventilated on 1.5–2.0% isoflurane in a mixture of air and oxygen and received either moderate fluid percussion or sham injury and were randomly assigned to one of four groups: aged-sham, a ged-TBI, young-sham, young-TBI. The rats were monitored for one hour post injury than decapitated and segments of the MCA were harvested. The MCA segments were mounted on an arteriograph, pressurized and the diameters were measured as intraluminal pressure was sequentially reduced from 100 to 20 mmHg in 20 mmHg decrements. MCAs in the young and aged sham groups showed normal, step-wise increases in diameter with decreases in intraluminal pressure from 100 to 40 mmHg. However there was an effect of age in the sham-groups at intraluminal pressures of 40 and 20 mmHg ($P < 0.05$). In young and aged TBI-groups, the MCA diameter was smaller compared to the sham-groups with each step-wise reduction in intravascular pressure. There was a significant effect of age on vasodilatory responses in the aged TBI group compared to the young-TBI group ($P < 0.05$) with the aged TBI group showing reduced vasoresponsiveness. In conclusion, vasodilatory responses to decreases in intravascular pressure in isolated MCAs were reduced in both TBI-groups compared to sham. In addition, the aged TBI-group demonstrated significantly reduced vascular reactivity compared to the young TBI-group, suggesting that reduced vascular reactivity after TBI may contribute to the worse outcome for older patients with TBI.

Key words
aging rat, middle cerebral arteries, TBI, vascular reactivity

C2-04

A COMBINATION THERAPY OF PHENYTOIN AND ETHOSUXIMIDE IMPROVED THERAPEUTIC BENEFITS AGAINST POST-TRAUMATIC NONCONVULSIVE SEIZURES

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Previously we reported that treatment with phenytoin (PHT) or ethosuximide (EXM) dose-dependently attenuated post-traumatic nonconvulsive seizures (NCS) induced in rats by penetrating ballistic-like brain injury (PBBI). The efficacious monotherapy dose ranges of the two drugs were identified to be 20–30 mg/kg (PHT) and 125–187.5 mg/kg (EXM), but moderate-severe sedation resulted. In this study isobolographic analysis was used to construct fixed dose ratios for the combination of PHT and EXM to determine if combined treatments could improve anti-seizure efficacy. All rats received frontal PBBI and were immediately subjected to post-injury EEG/video monitoring for 72 h for seizure detection. PHT and EXM were tested in pairs at the following fixed dose ratios: 1.8/5.5, 3.6/11.1, 7.2/22.2, or 14.4/44.4 mg/kg (PHT/EXM) and the treatments were given intravenously twice/day for three consecutive days, initiated 30 min post-injury. Control animals received matching vehicle treatments. Outcome measures included NCS incidence, frequency, duration, and onset latency. The results showed that

among the four dose ratios tested, the highest dose ratio (14.4/44.4 mg/kg) significantly reduced the overall incidence of NCS from 69% (vehicle group) to 29% (PHT + EXM group), decreased NCS frequency by 80% (Vehicle: 14.3 ± 5.5 NCS episodes/rat vs. PHT + EXM: 2.8 ± 1.3 episodes/rat), and shortened NCS cumulative duration by 84% (Vehicle: 502.8 ± 277 sec/rat vs. PHT/EXM: 82.5 ± 38.1 sec/rat). The PHT + EXM combination treatment also significantly delayed onset latency of NCS from 20 ± 4.4 h post PBBI (vehicle) to 53 ± 7.9 h (PHT + EXM). More importantly, compared to the effective monotherapy doses of PHT and EXM as mentioned above, the PHT + EXM combination therapy proved to be equally efficacious without overt sedation using 28% less PHT and 64% less EXM, which resulted in an additive effect as defined by the isobolographic analysis. This study supports the idea that combination therapy enhances the effectiveness of the drug constituents and provides improved therapeutic benefits by limiting potential side effects of individual drugs.

Key words
anti-seizure combination therapy, ethosuximide, penetrating brain injury, phenytoin

C2-05

THERAPEUTIC WINDOW FOR SELECTIVE BRAIN COOLING FOLLOWING PENETRATING BALLISTIC-LIKE BRAIN INJURY IN RATS

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Previous work has shown that 4 h selective brain cooling (SBC) initiated immediately following penetrating ballistic-like brain injury (PBBI) improves the injury-induced motor function in rats. The current study was designed to determine the delayed therapeutic window of SBC on motor function following PBBI. Unilateral frontal PBBI was produced in the right hemisphere of isoflurane anesthetized rats (10% injury severity level). SBC (34°C for 4 h) was induced via extraluminal cooling of the bilateral common carotid arteries, initiated at 2 h or 4 h after PBBI and continuously maintained under anaesthesia for 4 h. Sham and control rats (PBBI alone) were exposed to identical procedures as SBC (including being maintained under anaesthesia for up to 4 h) without the cooling of the brain. Neuroprotective efficacy was measured on the fixed-speed rotarod task to measure motor coordination and balance from 7 to 14 days post-injury (DPI). When SBC was delayed to 2 h post-PBBI ($SBC_{2\ h}$), significant improvement in motor function was detected at 7 DPI (mean rotarod latencies: Sham = 55 ± 3s; PBBI = 15 ± 3s; *PBBI + $SBC_{2\ h}$ = 28 ± 3s; *$p < .05$ $SBC_{2\ h}$ vs. PBBI) that was sustained out to 14 DPI (Sham = 58 ± 2s; PBBI = 19 ± 5s; *PBBI + $SBC_{2\ h}$ = 36 ± 3s; *$p < .05$ $SBC_{2\ h}$ vs. PBBI). When SBC was delayed to 4 h post-PBBI ($SBC_{4\ h}$), a trend towards improved performance was evident, but no significant improvement in motor performance was detected at either 7 DPI (Sham = 53 ± 1s; PBBI = 20 ± 1; PBBI + $SBC_{4\ h}$ = 23 ± 2s) or 14 DPI (Sham = 60 ± 0s; PBBI = 18 ± 5; PBBI + $SBC_{4\ h}$ = 22 ± 4s). No adverse effects were detected from SBC-treated rats regardless of when treatment was initiated. Collectively, these results suggest that SBC treatment provides therapeutic benefit in the absence of adverse effects, even when delayed up to 4 h post-injury. However, in order to achieve optimal therapeutic benefit SBC treatment should be initiated within 2 h post-injury.

Key words
function, hypothermia, penetrating brain injury, therapeutic window

C2-06

SELECTIVE ASTROCYTE OVEREXPRESSION OF HEME OXYGENASE-1 IS PROTECTIVE AFTER INTRACEREBRAL HEMORRHAGE

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Heme oxygenase-1 (HO-1) catalyzes the rate-limiting reaction of heme breakdown, and may have both antioxidant and pro-oxidant effects. In prior studies, HO-1 overexpression protected astrocytes from acute heme-mediated injury in vitro; conversely, unconditional HO-1 knockout was beneficial in vivo after ICH. In the present study, we tested the hypothesis that selective astrocyte overexpression of HO-1 improves outcome after intracerebral hemorrhage (ICH).

Male and female transgenic mice overexpressing human HO-1 driven by the GFAP promoter (GFAP.HMOX1) and wild-type FVB controls were injected with 25 μl autologous blood into the right striatum under stereotactic guidance. Blood-brain barrier disruption was assessed by Evans blue assay, and perihematomal cell viability by MTT assay. Neurological deficits were quantified by adhesive removal, corner, and elevated body swing tests, and by digital analysis of spontaneous cage activity. Mortality data were analyzed with Fisher's exact test; other data were analyzed with one-way ANOVA and the Bonferroni multiple comparisons test.

Striatal blood injection resulted in death of 25% of WT mice within 24 hours; all GFAP.HMOX1 mice survived ($P = 0.0048$). Striatal Evans blue leakage at 24 hours was 23.4 +/− 3.2 ng in surviving WT mice, compared with 10.9 +/− 1.8 ng in transgenics ($P < 0.001$). Perihematomal cell viability was reduced to 61 ± 4% of contralateral at 3 days in WT mice, v. 80 ± 4% in transgenics ($P < 0.05$). Focal neurological deficits were significantly reduced in GFAP.HMOX1 mice ($P < 0.001$), and spontaneous cage activity was increased ($P < 0.05$).

Selective HO-1 overexpression in astrocytes reduces blood-brain barrier disruption, perihematomal cell injury, neurological deficits, and mortality in an autologous blood injection ICH model. Genetic or pharmacologic therapies that transiently increase astrocyte HO-1 expression may be beneficial after ICH. The present findings contrast with the deleterious effects of acute HO-1 induction in other cell populations after ICH and chronic overexpression in neurodegenerative disease models, which are likely mediated by iron release.

Acknowledgment
Supported by NIH/NINDS R01NS079500.

Key words
heme, hemorrhage, iron, stroke

C2-07

DOSE-RESPONSE EVALUATION OF LEVETIRACETAM IN THE MIAMI FLUID PERCUSSION MODEL OF TRAUMATIC BRAIN INJURY: AN OBTT CONSORTIUM STUDY

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Levetiracetam is currently used after clinical traumatic brain injury (TBI) to target seizures. A few studies have suggested beneficial effects of levetiracetam following experimental TBI. Thus, it was chosen as the fifth drug to be tested by the multicenter consortium

Operation Brain Trauma Therapy (OBTT). The University of Miami site tested levetiracetam in our model of fluid percussion (FP) TBI. Male Sprague-Dawley rats were anesthetized and underwent moderate FP (1.8-2.1 atm) TBI. Rats were randomized into four groups and administered levetiracetam 15 min post-TBI. Animal groups were TBI-54 mg/kg (n = 12), TBI-170 mg/kg (n = 12), TBI-Veh (n = 12) or Sham (n = 12). Rats were tested on day 7 post-injury for sensorimotor function using the gridwalk and 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 histological assessment. One-way ANOVA was not significant for any of the sensorimotor tasks. For the hidden platform task, two-way repeated measures ANOVA for latency was significant for days and group. Both TBI levetiracetam treated groups exhibited lower latencies vs. TBI-Veh and Sham. There was a significant difference between groups for the probe trial ($p < 0.05$) with both levetiracetam groups performing at sham level. In the working memory task, latency repeated measures ANOVA was significant for trial ($p < 0.001$), but not group, or group x trial. However, both levetiracetam groups performed better on this task than TBI-Veh. Histopathological analysis for lesion volume was not significant between groups. Single dose treatment of levetiracetam early after FP TBI improved cognitive function but did not decrease histological damage. Levetiracetam shows promise for future studies assessing dosage optimization and therapeutic window after TBI, and evaluation in advanced models.

Support: US Army W81XWH-10-1-0623.

Key words
behavior, fluid percussion, neuroprotection, OBTT, traumatic brain injury

C2-08

DOSE-RESPONSE EVALUATION OF SIMVASTATIN IN THE MIAMI FLUID PERCUSSION MODEL OF TRAUMATIC BRAIN INJURY: AN OBTT CONSORTIUM STUDY

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Simvastatin (SIM) is a cholesterol lowering agent that has demonstrated other beneficial effects including reducing cytokine levels, brain edema, and improving histological and behavioral outcome after traumatic brain injury (TBI). SIM was chosen as the fourth drug to be tested by the multicenter consortium Operation Brain Trauma Therapy. The UM site tested SIM in our model of fluid percussion TBI. Male Sprague-Dawley rats were anesthetized and underwent moderate fluid percussion (FP; 1.8-2.1atm) TBI. Rats were randomized into four groups and administered SIM 3 hr post-TBI followed by daily PO dosing (14d). Animal groups were TBI-1mg/kg (n = 10), TBI-5mg/kg (n = 10), TBI-Veh (n = 10) or Sham (n = 10). 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 but was for left forelimb gridwalk footfaults ($p = 0.045$). TBI-Veh was significantly worse vs. sham ($p < 0.05$). For the hidden platform task, two-way repeated measures ANOVA for latency was significant for group × days ($p < 0.05$). TBI SIM 1mg/kg treated groups exhibited higher latencies vs. TBI-Veh and Sham. 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 × trial. Lesion volume or cortical volume loss was not significant between groups. We conclude that sustained treatment with SIM after FP produced a modest motor benefit but surprisingly led to either worse or unimproved cognitive function and did not decrease histological damage. Although several studies have shown an improvement with SIM treatment after TBI, other dosing strategies or routes of administration should be considered. Support: US Army W81XWH-10-1-0623.

Key words
behavior, fluid percussion, neuroprotection, OBTT, traumatic brain injury

C2-09

EVALUATION OF LEVETIRACETAM 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 TBI therapies. Levetiracetam, the fifth drug selected for testing by the OBTT, is an anti-epileptic drug that has previously demonstrated potent anti-seizure effects following penetrating ballistic-like brain injury (PBBI) and neuroprotective effects in other TBI models. Using the standard OBTT protocol, this study assessed the therapeutic efficacy of levetiracetam 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). Levetiracetam (West-Ward Pharmaceuticals, 54 or 170 mg/kg) was administered as a single IV infusion at 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 34 ± 9% (vehicle), 36 ± 13% (54 mg/kg), and 41 ± 11% (170 mg/kg) vs. sham. However, no significant improvement in motor outcome was detected following administration of levetiracetam. MWM results revealed significant deficits in all injury groups with the average latency to find the hidden platform (across testing days) increased by 123 ± 23% (vehicle), 108 ± 17% (54 mg/kg), and 127 ± 14% (170 mg/kg) vs. sham. Although no significant therapeutic effect was detected on spatial learning in the MWM acquisition trials, an intermediate therapeutic benefit was observed on the probe (missing platform) trials where animals treated with levetiracetam (both doses) did not differ from either sham or PBBI. Overall, the results of the current study indicate that a single post-injury infusion of levetiracetam does not confer significant therapeutic benefit in the PBBI model. However, given the promising results obtained in the other OBTT models, and positive independently obtained results using extended dosing in the WRAIR PBBI model, levetiracetam merits further study. Supported by U.S. Army Grant W81XWH-10-1-0623.

Key words
cognitive, Keppra, levetiracetam, motor, operation brain trauma therapy OBTT, traumatic brain injury TBI

C2-10

NEUROPROTECTIVE EFFECTS OF LEVETIRACETAM REQUIRES EXTENDED TREATMENT IN A RAT MODEL OF PENETRATING BALLISTIC-LIKE BRAIN INJURY

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Levetiracetam (Keppra) is a FDA approved anti-epileptic drug that has demonstrated neuroprotective effects in animal models of traumatic brain injury (TBI). Recently we demonstrated its anti-seizure effects on attenuating nonconvulsive seizures (NCS) induced by penetrating-ballistic-like brain injury (PBBI) in rats. The purpose of the current study was to determine whether a comparable treatment regimen would improve motor and cognitive function following PBBI. Our anti-seizure study established a significant dose-dependent reduction in NCS frequency and duration over a dose range of 25–100 mg/kg (*$p < .05$vs. PBBI/Veh). Based on those results, Levetiracetam (50 mg/kg, 2×the minimal effective anti-seizure dose) was delivered at 30 m and 8 h post-PBBI and twice/day thereafter for either 3 (LEV_{3D}) or 10 (LEV_{10D}) consecutive days. Motor and cognitive testing were conducted using rotarod at 7 and 10 days, and Morris water maze (MWM) from 13–17 days, post-PBBI. Results showed that the 3-day treatment regimen failed to provide significant neuroprotection on either motor or cognitive deficits. When the treatment was extended to 10 days, significant improvement in functional outcome was measured. Specifically, LEV_{10D}-treated rats showed significant improvement in rotarod performance (mean latency to fall at 20rpm: Sham = 43 ± 5s; PBBI/Veh = 10 ± 2s; LEV_{3D} = 18 ± 5s; *LEV_{10D} = 22 ± 5s; *$p < .05$ LEV_{10D} vs. PBBI/Veh). In addition, LEV_{10D}-treated animals displayed significantly shorter escape latencies in the MWM test than either LEV_{3D} or vehicle-treated PBBI animals (Sham = 28 ± 2s; PBBI/Veh = 63 ± 6s; LEV_{3D} = 66 ± 5s; *LEV_{10D} = 48 ± 5s; *$p < .05$ LEV_{10D} vs. PBBI/Veh or LEV_{3D}). Histopathological analysis revealed no differences across groups. Overall, Levetiracetam confers significant therapeutic benefit in the PBBI model when an extended 10 day dosing regimen is used. Collectively, our previous data showing potent anti-seizure effects of this drug, combined with the current results demonstrating significant neuroprotective effects, establish Levetiracetam as a prime target for further study and warrants consideration as a possible anti-seizure/neuroprotection drug candidate for combination therapy studies. Funded by the Army Combat Casualty Care Research Program.

Key words
Keppra, levetiracetam, traumatic brain injury TBI

C2-11

A NOVEL SMALL MOLECULE ANTI-CYTOKINE THERAPEUTIC ATTENUATES DOWNSTREAM COGNITIVE BEHAVIORAL DEFICITS IN A MOUSE MODEL OF TBI

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Evidence from clinical studies and preclinical animal models suggests that proinflammatory cytokine overproduction from activated glia is a potential driving force for pathology progression in traumatic brain injury (TBI). 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. Current studies are exploring optimal dosing in this model. For example, we are currently exploring the neurologic outcomes after multiple drug administrations post-injury during different time windows after injury. Initial results demonstrate that post-injury administrations of MW151 can completely ameliorate the cognitive deficits associated with the CHI. Our results continue to elucidate in standard preclinical models the critical aspect of dosing that includes repeat administration during the pharmacological mechanism of action time window. This knowledge is critical to the improvement of later phase 2 clinical trial designs and add to the criteria for Go/NoGo decisions on therapeutic development based on mechanisms of pathology progression that are characterized by proinflammatory cytokine overproduction. Support: KSCHIRT Grant 12-20A (LVE)

Key words
chemokine, closed head injury, cytokine, drug discovery, microglia, radial arm water maze

C2-12

DEFINING HOW TSG-6 IMPROVES LONG TERM MEMORY AFTER TRAUMATIC BRAIN INJURY IN MICE

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Administration of mesenchymal stem/stromal cells (MSCs) was previously observed to produce beneficial effects in models of TBI as well as other disease models. In several models, the beneficial effects were explained by the MSCs being activated to express TSG-6, a naturally occurring protein that modulates inflammation. In a mouse model of TBI produced by controlled cortical impact (CCI), we recently found (Watanabe et al. Neurobiol Dis 2013;59:86-99) that IV administration of recombinant TSG-6 during an initial mild phase of neuroinflammation decreased neutrophil extravasation, expression of matrix metalloproteinase 9 by endothelial cells and neutrophils, and the subsequent blood brain barrier leakage in secondary phase. It also decreased the lesion size at 2 weeks. Importantly, the acute administration of TSG-6 within 24 hour of TBI was followed 6 to 10 weeks later by improvements in memory, depressive-like behavior and the number of newly born-neurons. Here we found that 6 hr after IV administration of TSG-6, the recombinant protein was found in spleen but not at significant levels in other tissues. Also we found that plasma levels of S100β and pNF-H correlated with severity of CCI. The results provide a basis for defining in greater detail the beneficial effects in TBI of TSG-6, a protein that has a unique mode of action and that has not been observed to produce the adverse effects of steroids and other anti-inflammatory agents.

Key words
MSC, spleen, TBI, TSG-6

C2-13

A COMPARATIVE EVALUATION OF MEMANTINE AND TOPIRAMATE: NO EVIDENCE OF FUNCTIONAL RECOVERY FOLLOWING TRAUMATIC BRAIN INJURY

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The purpose of this study was to investigate and compare the therapeutic potential of two drugs, memantine and topiramate, on functional recovery utilizing clinically relevant doses. Memantine is a NMDA antagonist currently approved for use in Alzheimer's disease. Topiramate augments the function of GABA and is commonly used as an anticonvulsant. A multimodal behavioral assessment was conducted following induction of TBI. Subjects were randomly assigned to one of five groups: TBI + low dose memantine (5 mg/kg), TBI + high dose memantine (20 mg/kg), TBI + topiramate (10 mg/kg), TBI + vehicle (0.9% saline), and Sham + vehicle. Injuries were induced using a parietal controlled cortical impact (CCI) model. Treatments were administered via i.p. injections starting at 4 hours post-injury, followed by administrations every 12 hours for 48 hours. Motor and cognitive function was assessed using a variety of tasks used routinely in the lab. Gene expression was determined using microarray and gene ontology analysis in additional groups of animals at 24 h, 72 h and 7 days post-CCI. Neither memantine nor topiramate improved motor or cognitive function. Gene expression studies found that both drugs significantly affected dopaminergic synaptic transmission at 24 h and inflammatory response at 72 h after injury. These results indicate that while memantine and topiramate may provide benefits for other neurological conditions, their therapeutic potential following TBI appears limited.

Key words
behavior, CCI, memantine, pharmaceutical, recovery of function, topiramate

C2-14

EVALUATION OF SIMVASTATIN 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 TBI therapies. Simvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, is used clinically to reduce serum cholesterol. Additionally, Simvastatin has demonstrated potent anti-neuroinflammatory and brain edema reducing effects, showing promise in preclinical models of traumatic brain injury (TBI). This study assesed the potential therapeutic effect of oral Simvastatin 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. Simvastatin was dosed via oral gavage at 0 (vehicle), 1.0 and 5.0 mg/kg starting at 3 h post-injury and once/day thereafter for 14 days. Motor function was evaluated on the Rotarod and cognitive performance was evaluated on the Morris water maze (MWM). Brains were processed for histopathological analysis. Rotarod testing revealed motor deficits in all injury groups with overall mean latencies reduced by 39 ± 10% (vehicle), 32 ± 11% (1.0 mg/kg), and 30 ± 1% (5.0 mg/kg) with significant performance decrements detected in PBBI + vehicle animals only ($p < .05$ vs sham). In contrast, an intermediate treatment effect of Simvastatin (both doses) towards improved motor performace was evident at 10 days post-injury. Cognitive performance in the MWM revealed deficits in all injury groups with the average latency to find the hidden platform (across all testing days) increased by 70 ± 13% (vehicle), 68 ± 16% (1.0 mg/kg), and 87 ± 13% (5.0 mg/kg) vs. sham ($p < .05$). No significant therapeutic effects were detected on MWM parameters or on histological metrics. Overall, the results of this study indicate that sustained, oral administration of Simvastatin produces modest motor benefit but is ineffective in promoting significant neurofunctional and/or histopathological recovery in the PBBI rat model. Supported by U.S. Army Grant W81XWH-10-1-0623

Key words
neuroprotection, OBTT, PBBI, simvastatin, TBI

C2-15

EARLY GLUCOSE SUPPLEMENTATION FOLLOWING CONTROLLED CORTICAL IMPACT INJURY DOES NOT ALTER OXIDATIVE METABOLISM 24 HRS POST-INJURY

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Following TBI, extracellular glucose levels are frequently reduced and predictive of poor outcome suggesting that endogenous fuels may not be sufficient to meet metabolic demands. We reported that exogenous glucose treatments over 6 hrs after controlled cortical impact (CCI) injury resulted in improved cerebral metabolism and neuronal survival at 24 hrs after injury. The purpose of this study is to determine if glucose supplementation immediately after injury influences the activity of metabolic pathways associated with oxidative metabolism and the intracellular redox state. Sixteen male rats underwent a moderate-severe CCI with an additional 8 rats receiving anesthesia only (Control). CCI-injured animals received an i.p. injection of glucose (CCI-Glc; 2000 mg/kg, n = 8) or 8% saline (CCI-SAL; n = 8) at 0, 1, 3, 6 and 23 hrs post-injury. At 24 hrs post-injury animals were infused with [1, 2 $^{13}C_2$] glucose for 60 minutes. Following infusion, animals were euthanized and extracts of the injury cortex and hippocampus were prepared. Proton decoupled ^{13}C NMR spectra were obtained on a Bruker Avance 500 MHz spectrometer. The amount of ^{13}C in each metabolite isotopomer was quantified using sodium 3-(trimethylsilyl) propionate. Between group differences were measured using a one-way ANOVA with a post-hoc Bonferrroni comparison. Compared to controls, the total amount of ^{13}C labeled glutamate ($p < 0.001$) and glutamine ($p = 0.05$) was significantly lower in the injured hemisphere of CCI-injured groups. Glucose metabolism via the pentose phosphate pathway (PPP) trended lower in the CCI-Glc group, but did not reach significance ($p = 0.18$ vs. control). These results indicate that glucose supplementation beginning immediately post-CCI did not improve neuronal and astrocyte oxidative metabolism (i.e. ^{13}C enrichment of glutamate and glutamine), nor did glucose treatments significantly impact cellular redox state (i.e. PPP) at 24 hrs post-injury.

Key words
13C spectroscopy, glucose, intracellular redox state, oxidative metabolism

C2-16

NEUROPROTECTIVE EFFECTS OF NOVEL THERAPEUTIC NNZ-2591 FOLLOWING PENETRATING TBI

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NNZ-2591 is a synthetic analog of the neuropeptide cyclic glycine-proline (cGP), an active metabolite of the neuropeptide glycine-proline-glutamate (GPE) or (1-3)IGF-1 which is cleaved from the n-terminus of IGF-1. NNZ-2566, a synthetic analog of (1-3)IGF-1, is currently in clinical trials for TBI, Fragile X syndrome, and Rett syndrome. NNZ-2566 reduces post-injury inflammatory mechanisms and preserves cognitive and motor system function following penetrating ballistic-like brain injury (PBBI). While NNZ-2566 is approximately 45–50% orally bioavailable, NNZ-2591 exhibits 100% oral bioavailability. Here, we investigate whether, like NNZ-2566, NNZ-2591 has anti-inflammatory activity, and if it regulates genes that govern synaptic plasticity following PBBI. Groups tested: Sham + vehicle, PBBI + vehicle, PBBI + NNZ-2591 (30 mg/kg by oral gavage 30 min post-injury and again once daily until endpoint). Ipsilateral brain tissue containing the injury tract was collected 24 h, 72 h and 7 days post-injury ($n = 10$). IL-1beta and IL6 levels were evaluated by ELISA. IL1beta cytokine levels were increased by PBBI: 24 h (72%, $p < 0.001$); 72 h (48%, $p < 0.01$); 7 days (17%, $p < 0.05$). NNZ-2591 did not decrease IL-1beta levels at 24 h or 72 h but decreased levels at 7 days (7%, $p < 0.05$). IL6 levels were increased by PBBI at 24 h (400%, $p < 0.001$) but not 72 h or 7 days. NNZ-2591 decreased IL6 levels at 24 h (33%, $p < 0.05$). In addition, at 7 days NNZ-2591 reduced IL6 levels below both PBBI and sham levels 17% ($p < 0.05$) and 22% ($p < 0.01$), respectively. In separate animals, microarrays of 83 genes involved in synaptic plasticity were evaluated at 24 h post-injury ($n = 4$). Gene array analysis indicated that many genes were altered by PBBI. NNZ-2591 mitigated PBBI induced changes for select genes. For example, at 24 h post PBBI, NNZ-2591 increased mRNA levels of *ppp3ca* (1.4 fold, $p < 0.05$) but decreased *tnf* (-1.713 fold, $p < 0.05$) compared to PBBI + vehicle. Continued analysis will likely identify additional inflammatory or neuroplasticity genes altered by NNZ-2591. Collectively, these results indicate that NNZ-2591 has neuroprotective and anti-inflammatory effects following severe TBI. Its excellent bioavailability makes it a potentially promising treatment for mild, moderate, or severe TBI.

Key words
neuroprotection, NNZ-2591, PBBI, severe TBI

C2-17

THE DEVELOPMENT OF NON-CONVULSIVE SEIZURES FOLLOWING MILD TRAUMATIC BRAIN INJURY WITH MILD HYPERTHERMIA IN THE RAT

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Post-traumatic non-convulsive seizures represent an important clinical entity. Recent literature suggests that the majority of seizures following traumatic brain injury (TBI) are non-convulsive. Presently, few experimental studies have investigated the pathophysiology of post-traumatic non-convulsive seizures after mild TBI. Our laboratories have recently reported that mild elevations in brain temperature that may occur during periods of strenuous exercise or other activities can worsen outcome after mild TBI. This study therefore characterized the impact of mild elevations of temperature on the development of post-traumatic seizure events. The Marmarou weight drop model of closed-head traumatic brain injury was used at a mild level of severity. Three groups of animals were tested: sham ($n = 5$), TBI-normothermia ($n = 4$), TBI-hyperthermia ($n = 4$). Normothermia was maintained at 37°C and hyperthermia animals at 39°C. Animals were monitored for temperature for two hours following trauma. One hour video electroencephalography was performed at 12-weeks post-injury, and power spectral analysis was performed in MATLAB using custom-written software EEGgui. Behavioral testing was performed at baseline, 1-week post-injury, and 12-weeks post-injury. Animals were transcardially perfused at 12 weeks for histopathological analysis. Preliminary electrophysiology data suggests an increase in seizure susceptibility among animals with hyperthermia. Epileptic events were characterized by periodic increases in ECoG power across multiple frequency bands. Behavioral testing in these mildly traumatized animals demonstrates few statistically significant differences among latencies in the watermaze hidden platform, probe, and working memory tasks. The impact of hyperthermia on the extent of post-traumatic mild diffuse brain injury appears to be subtle. However, mild hyperthermia appears to make neurons more susceptible to seizure events, particularly non-convulsive seizures. Studies are currently in progress to next determine the consequences of repetitive episodes of mild TBI on the electrophysiological and behavioral outcomes using these innovative monitoring approaches. Supported by W81XWH-12-1-0618.

Key words
non-convulsive seizure, traumatic brain injury

C2-18

DIFFERENTIAL EFFECTS OF CX3CR1 OR CCR2 DELETION IN HIPPOCAMPAL INFLAMMATORY RESPONSE FOLLOWING TRAUMATIC BRAIN INJURY

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CNS infiltrating monocytes/macrophages can be reliably divided into two distinct subpopulations based upon their cells surface expression of two chemokine receptors, CX3CR1 or CCR2. Recent work has shown that TBI creates a permissive environment for the infiltration of systemic or circulating immune cells into the brain following injury. However, in the context of TBI-initiated neuroinflammatory response, the relative contribution of $CCR2^+$ or $CX3CR1^+$ monocytes/macrophages remains elusive. Importantly, genetic deletion of CCR2 or CX3CR1 depletes circulating levels of their respective monocyte subpopulations, which has shown differential effects in various neurodegenerative disease models. Herein, we examined the effect of CCR2, CX3CR1, or combined genetic deletions on the neuroinflammatory response in the hippocampus following TBI. Using the controlled cortical impact model, 3 month old $CX3CR1^{GFP/GFP}$, $CCR2^{RFP/RFP}$, and $CX3CR1^{GFP/GFP}CCR2^{RFP/RFP}$ mice were injured in the parietal lobe and sacrificed 24 hours following injury. Ipsilateral hippocampi were dissected and processed for RNA extraction to quantify the gene expression of multiple

markers associated with inflammatory response and macrophage polarization. Our data show that genetic deletion of CX3CR1 or CCR2 differentially affects the expression of various inflammatory and macrophage polarization markers. These data may suggest that selectively targeting distinct populations of infiltrating monocytes could differentially affect the TBI-induced inflammatory response.

Funding
This work was supported by the NIH R01 CA133216 (S.R.), R21 AG042016 (S.R.), and Alzheimer Association IIRG-11-202064 (S.R.)

Key words
CCR2, CX3CR1, hippocampus, polarization

C2-19

PDE4B INHIBITION RESCUES CHRONIC MEMORY DEFICITS FOLLOWING TRAUMATIC BRAIN INJURY

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Learning and memory deficits are the most common neurocognitive consequences associated with chronic traumatic brain injury (TBI), but poorly understood from a mechanistic viewpoint. Our previous study has shown that a pan-phosphodiesterase 4 (PDE4) inhibitor rescues cognitive deficits following TBI. However, pan-PDE4 inhibitors are hampered by unwanted side effects and the development of more isoform-selective inhibitors would greatly improve translational development. We have found that TBI induces expression of the subfamily isoform PDE4B2. Thus, we hypothesized that treating animals with a subtype-specific PDE4B inhibitor could reverse the cognitive deficits induced by TBI. To test this hypothesis, adult male Sprague Dawley rats received sham surgery or moderate parasagittal fluid-percussion brain injury. After 3 months of recovery, animals were treated with the selective PDE4B inhibitor A33 prior to cognitive training. Animals were trained in cue and contextual fear conditioning, spatial reference memory and spatial working memory.

TBI-induced deficits in cue and contextual fear conditioning were significantly reversed with A33 treatment. Furthermore, hippocampal-dependent spatial memory was enhanced in TBI animals treated with A33 as compared to TBI animals treated with vehicle. Additionally, administration of A33 was also effective in rescuing working memory performance in TBI animals and restored their performance to non-injured levels. To further understand the underlying mechanisms of these memory impairments, basal synaptic transmission and hippocampal long-term potentiation (LTP) of the Schaffer collateral pathway in area CA1 were studied 3 months after TBI or sham surgery. Hippocampal slices from TBI animals showed a significant reduction in basal synaptic transmission and impairment in expression of LTP as compared to sham surgery animals. We are currently analyzing the effects of A33 on these electrophysiological changes. These results indicate that a subtype-selective PDE4B inhibitor may be a potential cognitive enhancer and reverse chronic cognitive dysfunction following TBI.

Supported by: The Miami Project to Cure Paralysis, NIH/NINDS NS056072 and NIH/NINDS NS069721

Key words
fluid-percussion injury, learning and memory, phosphodiesterase 4B, synaptic plasticity

C2-20

EFFECTS OF PROPHYLACTIC OMEGA-3 FATTY ACID TREATMENT ON TBI-INDUCED MICRORNA EXPRESSION

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Psychiatric co-morbidities, such as depression, often develop after traumatic brain injury (TBI) and exacerbate the diminished quality of life and disability caused by the trauma. Preliminary studies suggest that TBI-induced changes in microRNA (miRNA) expression may increase the risk of developing depression. Recent reports indicate that prophylactic treatment with omega-3 polyunsaturated fatty acids (ω-3 PUFAs) ameliorates both injury severity and cognitive decline in animal models by acting as a neuroprotective agent. In humans, a deficiency in dietary ω-3 PUFAs may cause or worsen depression, whereas supplementation with ω-3 PUFAs may relieve depressive symptoms. We hypothesized that prophylactic treatment with ω-3 PUFAs will ameliorate the effects of TBI on miRNA expression. In our rodent model of fluid-percussion TBI, rats were prophylactically dosed with ω-3 PUFAs (Menhaden fish oil) in their diet continuously four-weeks prior to the infliction of injury. Control animals received a diet consisting of 7% by weight soybean oil chow. Blood was collected from the jugular vein of all animals prior to dietary dosing, 24 h before/after TBI, and 4-weeks after treatment. Expression levels of circulating miRNAs were determined by quantitative RT-PCR. Three weeks post-TBI, depression-like behavior (reduction in immobility time) of control and TBI animals was assessed using the Forced Swim Test. At the conclusion of the study, 4 weeks after TBI, animals were sacrificed for histopathological and molecular analysis by qPCR, which included miRNA expression in laser-microdissected brain regions associated with depression (i.e., hippocampus, nucleus accumbens, prefrontal cortex, and suprachiasmatic nucleus). Examination of miRNA expression levels in depression-related brain regions has provided compelling evidence to suggest that TBI causes a dysregulation in miRNAs that regulate genes associated with cell survival and cell death. A subset of these miRNAs showed differential expression in serum samples correlating with that of depression-associated brain regions. This subset of circulating miRNAs might serve as a non-invasive biomarker of injury progression and effective prophylactic treatment in human TBI patients.

Key words
cell survival, depression, microRNA, TBI

C2-21

PHOSPHODIESTERASE 4B INHIBITION AS A THERAPEUTIC FOR TRAUMATIC BRAIN INJURY

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The neuroprotective benefits of cAMP elevation, via pan-PDE4 inhibition, have been used as a therapeutic strategy in many CNS injury models, such as spinal cord injury (SCI), cerebral ischemia, and traumatic brain injury (TBI). Knock-out studies have indicated that the anti-inflammatory effects of pan-PDE4 inhibition are primarily attributed to the PDE4B subfamily. Pro-inflammatory

stimuli, such as lipopolysaccharide and tumor necrosis factor, induce expression of the PDE4B isoform, PDE4B2, in macrophages, astrocytes and microglia. This upregulation of PDE4B2 is also observed after SCI and TBI, and may be involved in a positive feedback loop, potentiating the inflammatory response. However, whether this increase in PDE4B2 expression is localized to inflammatory cells after TBI, and whether PDE4B inhibition improves histopathological outcome after TBI is unknown. To address these questions, 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 leukocytes isolated from the ipsilateral parietal cortex and hippocampus for PDE4B2 expression at 3 hrs and 24 hrs after TBI. We found that PDE4B2 was significantly elevated in microglia and infiltrating leukocytes at 24 hrs, but not 3 hrs, after TBI. To determine how PDE4B inhibition affects pathology after TBI, animals received vehicle (5% DMSO in saline) or a PDE4B inhibitor, A33, at 0.3 mg/kg (i.p.) at 30 minutes post-TBI and once a day for 3 days. Pathology was evaluated in serial brain sections stained with hematoxylin and eosin. We found that acute PDE4B inhibition significantly reduced cortical contusion volume at 3 days post-injury. These results suggest that the PDE4B subfamily may be involved in modulating the inflammatory response after TBI.

Supported by The Miami Project to Cure Paralysis and NIH/NINDS NS069721.

Key words
inflammation, PDE4B, phosphodiesterase, traumatic brain injury

C2-22

P75NTR MEDIATES LEUKOCYTE TRAFFICKING IN THE BRAIN AFTER TRAUMATIC BRAIN INJURY (TBI) IN MICE

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TBI leads to progressive brain damage resulting in chronic neurological deficits, which may be partly mediated by pro-inflammatory responses in both injured brain and the circulation. This acute inflammation may involve myeloid trafficking into injured brain. Previously, we found that blocking the p75NTR-signaling pathway by SARA, a selective p75NTR antagonist, inhibits tissue damage and increases behavioral outcome after TBI in rats. Strikingly, blocking p75NTR-signaling reduces microglia activation, suggesting p75NTR's involvement in local inflammatory responses after TBI.

Since some evidence implicates p75NTR in peripheral immune function, we examined whether p75NTR mediates leukocytes trafficking into the injured brain. To identify peripheral leukocytes, we used $CCR2^{RFP/+}$ Tg mice. We found that blocking p75NTR-signaling with daily injections of SARA inhibited trafficking of CCR2+ monocytes into injured brain as measured by RFP positive signal. Consistently, blocking p75NTR signaling increased surviving tissue at 7D post-injury. Using WT mice, we confirmed that p75NTR-signaling reduced CCR2+/CD45+ positive signals in the injured brain by immunostaining. Because CCR2 is down-regulated in the tissue (Saederup et al., 2010), we also examined the infiltration of F480+ and CD11c+ cells in the injured WT brain by immunostaining. Consistently, SARA treatment reduced trafficking of F480+/CD45+ cells as well as CD11c+/CD45+ cells in injured brain. Interestingly, SARA treatment also reduced CCR2+ monocytes in the circulation 7D after TBI as measured by flow cytometry. These data suggest that p75NTR inhibits leukocyte trafficking in the injured brain by attenuating leukocyte activation.

Together, our findings suggest that blocking p75NTR reduces inflammatory monocytes in the circulation as well as in the injured brain, and this may contribute to SARA's therapeutic effects after TBI.

Supported by Sanofi R&D., NS038079, UCSF/BASIC pilot funds

Key words
inflammatory response, leukocyte trafficking, p75NTR, traumatic brain injury

C2-23

THE EFFECT OF 7, 8-DIHYDROXYFLAVONE (7,8-DHF) FOLLOWING TRAUMATIC BRAIN INJURY

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Following TBI, the brain undergoes series pathological changes compromising neural survival and plasticity which contribute to functional deficits. Treatment that has neuroprotective effect and promotes neural plasticity is desirable. A flavone derivative, 7,8-DHF is a recently identified small molecule TrkB agonist which binds with high affinity and specificity to the TrkB receptor, activating its downstream signaling cascade with functions similar to BDNF. Compared to BDNF, 7,8-DHF has more advantages as it can pass the blood-brain barrier and is bioactive when given intraperitoneally, subcutaneously or orally. In this study, we assessed the optimal time window for 7,8-DHF treatment in imporving post-TBI functional recovery and synaptic plasticity following a focal brain injury. In this study, adult male Sprague-Dawley rats were used. Animals were subjected to a moderate cortical impact injury. At 2 hr, 2 or 5 days following injury, 7,8-DHF was administrated i.p. at the dose of 5mg/kg. Thereafter, 4 more daily single doses were given (day 0–4; day 2–6; day 5–9). Sensorimotor functions wre tested using Beam Walking and Rotarod tests. Cognitive functions were assessed using Fear Conditioning tests and Morris Water Maze latency and probe trial tests. Animals were sacrificed at 15 or 28 days post-injury. Brain sectons were processed for histological examination to assess lesion volume, neuronal cell survival, neurogenesis and synaptic plasticity. We found that following TBI, 7,8-DHF given at day 0–4 but not 2–6 or 5–9 ameliorated motor deficits in both beam walking and rotarod tests. In MWM and fear conditioning tests, injured animals with 7,8-DHF treatment at day 0–4 or 2–6, but not 5–9 post-injury had improved cognitive functional recovery compared to injured animals which received vehicle treatment. Further studies examining lesion volume, hippocampal neuronal cell survival, post-TBI neurogenesis and synaptic plasticity are ongoing. Our data suggest that 7,8-DHF has neuroprotective effects improving both motor and cognitive functional recovery when given at early time post-injury. It also promotes neural plasticity enhancing cognitive recovery when given at early synaptic regeneration stage.

Key words
7, 8-DHF, cognitive function, neural plasticity, neuroprotection, traumatic brain injury, TrkB agonist

C2-24

TRANSPLANTED NEUROSPHERES FROM GENETICALLY MODIFIED ADULT BONE MARROW AFTER CCI: EFFECTS ON INJURY SIZE AND TRANSPLANT SURVIVAL

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A potential treatment for traumatic brain injury is transplantation of adult bone marrow-derived mesenchymal stem cells (BMSC). Although previous studies have transplanted undifferentiated BMSC following TBI, our lab transplanted neurospheres derived from BMSC genetically modified with the intracellular domain of Notch1 and neo-resistance genes. These modified BMSC were transduced with a GFP lentivirus and grown under non-adherent conditions to promote formation of neurospheres that were transplanted one-week post-controlled cortical impact (CCI) in the rat. Transplants were placed in the injured cortex or striatum below the injury. Previous data demonstrated that transplanted neurospheres decreased sensorimotor deficits out to one month post-transplant. Behavioral enhancement was better in rats with striatal vs. cortical transplants. The current study examined whether these behavioral results could be explained by differences in transplant survival or neuroprotection. Brain tissue from these animals was analyzed one month post-injury using Neurolucida. Survival of stem cells was measured qualitatively with a rating scale for GFP positive cells. Neuroprotection or replacement of cells post-injury was measured via an analysis of remaining cortical area (μm^2) in sections containing the forelimb sensorimotor cortex. The volume of remaining cortex was obtained by multiplying total area by the distance between sections, $0.24\,mm^2$. ANOVA demonstrated that striatal neurosphere transplants showed better survival (i.e. presence of more GFP positive cells) than cortical transplants ($p < 0.05$). ANOVA of cortical volume indicated that there was no significant difference between striatal and cortical neurosphere transplants ($p > 0.05$ compared to CCI only). Results indicated that striatal neurosphere transplants following TBI have better survival than cortical transplants, but the neurosphere transplants in either region have no effect in reducing contusion size through neuroprotection or replacement, suggesting that the behavioral enhancement seen is due to other factors such as trophic factors.

Key words
cortical volume, neurospheres, sensorimotor cortex, TBI

C2-25

INVESTIGATION OF THE EFFECTS OF CARBOXYFULLERENE NANOPARTICLES ON THE CEREBRAL VASCULATURE AFTER FLUID PERCUSSION INJURY

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Traumatic brain injury (TBI) causes an increase in reactive oxygen species (ROS) that can cause cerebral vascular dysfunction. Reducing ROS levels can preserve vascular function and improve outcome after injury. Our preliminary results suggested that treatment with the carboxyfullerene nanoparticle DF-1 improved Morris water maze performance after TBI. DF-1 is an antioxidant that is capable of reducing ROS levels. Here we tested the hypothesis that improved behavioral outcome after DF-1 treatment was due in part to a reduction in TBI-induced cerebral vascular dysfunction.

Male Sprague-Dawley rats ($n = 40$) were anesthetized with isoflurane (1.5%), prepared for parasagittal fluid percussion TBI and randomly assigned to receive sham, moderate TBI alone or TBI followed by treatment with 10, 25 or 50 mg/kg DF-1 one hour post-injury ($n = 8$ animals/group). Measurements of cerebral perfusion (laser Doppler flowmetry, LDF) and mean arterial pressure (MAP) were made from 30 minutes prior to injury and continued for two hours following injury. Cerebral vascular resistance (CVR) was calculated as $CVR = MAP \times LDF^{-1}$.

MAP was significantly increased ($P < 0.05$) by all three doses of DF-1 compared to sham and injured animals. The 25 and 50 mg/kg doses produced greater increases than the 10 mg/kg dose. Cerebral perfusion was reduced with treatment. Lower doses (10 and 25 mg/kg) were associated with greater reductions in perfusion compared to injured animals and those treated with 50 mg/kg doses ($P < 0.05$). CVR was significantly increased by DF-1 with higher doses producing greater increases ($P < 0.05$).

These results demonstrate that DF-1 treatment increased MAP and CVR while reducing cerebral perfusion. Larger doses seem to return cerebral perfusion closer to baseline compared to lower doses. Reduced cerebral perfusion would have a negative effect on outcome after injury. This leads us to conclude that DF-1 might be conferring benefits on the cellular or molecular level that out weigh the effects that might be caused by a reduction in cerebral perfusion.

Key words
nanotechnology, TBI

C2-26

THE EMERGING ROLE OF AMP-ACTIVATED PROTEIN KINASE IN TBI AND ITS PHARMACOLOGICAL REGULATION BY S-NITROSOGLUTATHIONE

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A growing body of research indicates that traumatic brain injury (TBI) patients and animal models exhibit bioenergetic and metabolic abnormalities, blood-brain barrier (BBB) disruption neurobehavioral deficits. We hypothesized that AMPK, a sensor and regulator of energy balance, activation is associated with peroxynitrite-mediated endothelial dysfunction in the acute phase whereas its activation in the chronic phase up regulates the process of neurorepair. Therefore, we investigated the efficacy S-nitrosoglutathione (GSNO) which invokes functional recovery and reduces levels of peroxynitrite.

TBI was induced by controlled cortical impact (CCI) in adult male rats. GSNO (0.05 mg/kg) and compound c (5 mg/kg) were administered at two hours after CCI and daily thereafter. In addition to functional recovery, the following neurovascular protection and neurorepair mediators were evaluated: AMPK, peroxynitrite, eNOS, BBB leakage, edema, HIF-1α/VEGF and vessel density.

Treatment with AMPK inhibitor compound c and BBB inducing agent GSNO after TBI reduced peroxynitrite levels, inhibited BBB disruption and edema formation. The treatment with GSNO also reduced the expression of AMPK and eNOS in the acute phase. However, a chronic treatment with compound c had adverse effect on functional recovery. In contrast, chronic GSNO treatment of TBI not

only increased HIF-1α/VEGF and vessel density but also improved neurobehavioral functions.

Oxidative stress (peroxynitrite) causes a sustained activation of AMPK in the acute phase leading to BBB disruption and edema. On the other hand, pharmacological inhibition of AMPK activity in the chronic phase hampers functional recovery. These observations provided us rationale for the use of GSNO which protected BBB integrity by reducing peroxynitrite in the acute phase. In the chronic phase, GSNO aids in functional recovery by up regulating the neurorepair-associated HIF-1α/VEGF pathway and angiogenesis. GSNO is a natural molecule and its exogenous administration has not shown toxicity or side effects in humans.

The study was supported by grant from the NIH NS-72511.

Key words
AMPK, functional recovery, GSNO, HIF-1 alpha, neurorepair, vessel density

C2-27

KNOCKOUT OF CYCLOPHILIN D PREVENTS INCREASED INTRINSIC AND SYNAPTIC NEURONAL EXCITABILITY AFTER MILD TRAUMATIC BRAIN INJURY (MTBI)

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Mitochondria are central to Ca^{2+} homeostasis. Dysfunction resulting in mitochondrial permeability transition pore (MTP) opening has been reported after mTBI. Cyclophilin D is an integral part of the MTP. Recently our group has found that the extent of axonal injury was diminished in neocortex after mTBI in cyclophilin D knockout (KO) mice. Here we tested whether this KO could also provide protection from the increased intrinsic and synaptic neuronal excitability previously described. In these experiments a central fluid percussion injury was given to 6–8 week old YFP-h mice. Whole cell patch clamp recordings from axotomized (AX) and intact (IT) YFP + layerV pyramidal neurons were made after 1–2 day survival. Action potentials (AP) were recorded in current-clamp mode while neurons were maintained at − 60 mV. Excitatory post synaptic currents (EPSCs) were recorded in voltage-clamp mode with neurons held at − 70 mV. While AP are increased in amplitude in AX at 1–2 days and in IT at 1 day after injury, in KO mice this increase was prevented. After mTBI in KO mice, the amplitude of AP in IT and AX neurons was not different (1–2 day survival) from that in naïve KO mice (ANOVA, $p > 0.05$, $n \geq 9$ cells). There was however a trend towards an increased AP amplitude for IT neurons at 1day ($p < 0.5$ with t-test). Thus, there may be additional factors that contribute to the alteration of this intrinsic property. This KO also prevented the changes in EPSCs previously observed after mTBI. The frequency and amplitude of spontaneous and miniature (1 mM TTX in bath) EPSCs were not different between naïve and mTBI at 1–2 day survival times for AX and IT neurons from KO mice (ANOVA, $p > 0.05$, $n \geq 8$ cells). Thus, the CypD-mediated mitochondrial permeability transition pore is linked to the cellular and synaptic perturbations observed in the pathogenesis of mTBI. These data support the idea that therapies aimed at mitochondrial protection should prove clinically useful. Supported by NIH grant NS077675. Mouse strain supplied by Michael Forte, Vollum Institute, OHSU.

Key words
action potential, cyclophilin D, excitatory synaptic transmission, mitochondria

C2-28

THE NRF2-ARE PATHWAY AS A THERAPEUTIC TARGET IN TRAUMATIC BRAIN INJURY: GENETIC AND PHARMACOLOGICAL APPROACHES FOR NEUROPROTECTION

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The pathophysiological importance of oxidative damage after traumatic brain injury (TBI) has been extensively demonstrated in experimental models. The transcription factor Nrf2 mediates antioxidant genes by binding to antioxidant response elements (ARE) within DNA and upregulating these genes creating a pleiotropic cytoprotective-defense pathway. Previously, we determined the post-TBI time-course of Nrf2-ARE mediated gene expression in cortex and hippocampus utilizing the unilateral controlled cortical impact (CCI) model. Increased Nrf2-ARE mediated expression closely followed that of post-TBI oxidative damage markers 4-HNE and 3-NT (Miller et al., J. Neurotrauma, March 2014, in press). Moreover, pre-treatment 48 hours prior with Nrf2-ARE activating drug carnosic acid (CA) (single 1.0 mg/kg i.p. administration) provides protection to cortical mitochondria bioenergetics after exposure to the toxic aldehyde 4-HNE *ex vivo* that was accompanied by decreased 4-HNE bound to mitochondrial proteins (Miller et al., Free Rad. Biol. Med. 57:1-9, 2013). In addition, we conducted a post-TBI dose response of CA and found that a single 1.0 mg/kg i.p. administration 15 minutes post-TBI reduced levels of oxidative damage markers in cortex and hippocampus. In the current study, we demonstrate for the first time that CA can significantly improve ($p < 0.05$) cortical mitochondrial respiratory function at 24 hours post-TBI as compared to vehicle animals which is accompanied by a concomitant reduction in oxidative damage to mitochondrial proteins. Additionally, we have found that oxidative damage is increased in Nrf2-knockout mice but attenuated in mice overexpressing Nrf2. Current studies are determining if genetic manipulation attenuates behavioral deficits and neurodegeneration. Pharmacological studies are also assessing the therapeutic window of CA wherein initial administration is delayed to 1, 4, or 8 hours post-TBI. Furthermore, an evaluation of CA's capability to attenuate behavioral deficits and neurodegeneration post-TBI is also underway. These studies will determine if targeting the Nrf2-ARE pathway post-TBI has clinical relevance.

Key words
gene expression, neuroprotection, oxidative stress, TBI, transcription factor

C2-29

EFFECTS OF ETHYL PYRUVATE ON MARKERS OF OXIDATIVE STRESS AND GLYCOLYTIC FUNCTION AFTER TRAUMATIC BRAIN INJURY

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The current study examined potential mechanisms by which ethyl pyruvate (EP) improves cerebral glucose metabolism and reduces neuronal injury after experimental traumatic brain injury (TBI). Adult male Sprague-Dawley rats received sham injury or TBI (contusion) to the left parietal cortex followed by injections of EP (40 mg/kg, IP) or no treatments at 0, 1, 3 and 6 h. At 7 h post-injury left cortical tissue was harvested and processed for Western blots, levels of nicotinamide adenine dinucleotide (NAD^+) and GAPDH enzyme activity. Protein

levels for GAPDH were not affected by TBI or EP treatments. Cytosolic levels of heme oxygenase 1 (HO-1) protein and nuclear levels of poly(ADP)-ribosylated (PAR) proteins were significantly increased above sham levels in the TBI ($p < 0.05$ and $p < 0.01$, respectively) and TBI-EP ($p < 0.01$, $p < 0.001$, respectively) groups, but these markers of oxidative stress did not differ between the TBI and TBI-EP groups (n = 4-5/group). The NAD^+ levels in cytosolic fractions were significantly reduced by TBI ($p < 0.001$ vs. sham) and, while NAD^+ levels were higher in TBI-EP compared to TBI, NAD^+ remained significantly reduced in the TBI-EP group compared to sham operates ($p < 0.01$; n = 11-12/group). GAPDH enzyme activity in cytosolic fractions was significantly reduced by TBI ($p < 0.01$ vs. sham). EP treatments after TBI improved GAPDH enzyme activity to a level not significantly different from sham levels, but this improvement was also not significant compared to TBI only controls (n = 11-12/group). These findings are consistent with concepts that TBI-induced activation of nuclear poly(ADP-ribose) polymerase-1 (PARP-1) consumes cytosolic NAD^+ to form PAR polymers, and the reduced NAD^+ impacts on redox reactions including glycolysis. The ability of EP treatments to mildly improve cytosolic levels of NAD^+ and GAPDH enzyme activity by 7 h post-TBI may explain how EP improves cerebral metabolic rates for glucose at 24 h after injury.

Support: NS058489 and UCLA BIRC

Key words
CCI, GAPDH enzyme, NAD, oxidative stress, pyruvate

C2-30

REMOTE ISCHEMIC PRECONDITIONING (RIPREC) PROTECTS FROM TRAUMATIC BRAIN INJURY (TBI)

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TBI is a major cause of disability, which needs a safe therapy suitable for use in fileds, pre-hospital and clinical settings. We previously reported that remote ischemic conditioning (RIC) during stroke improves cerebral blood flow (CBF) and functional outcomes (Hoda et al). In this work, we hypothesized that RIPreC will prevent post-TBI ischemia, injury and inflammation, and will upregulate endogenous protection via AMP-activated kinase (AMPK).

Bilateral RIPreC for 7 days before TBI (RIPreC + TBI), RIPreC sham with TBI (TBI-group) or related sham procedures (Sham-group) were performed as reported (Hoda MN et al 2014) in WT C57/B6 and AMPK alpha1 knock out (AMPK$\alpha 1-/-$) male mice ($\sim$4-mo; n = 5/group). TBI was performed by severe controlled cortical impact. CBF was determined using laser speckle imager. Results were compared by t-test and ANOVA, as needed ($P < 0.05$).

Acute CBF immediately after TBI was not significantly different in the TBI-group vs. RIPreC + TBI. However, RIPreC + TBI-group showed significant improvement in CBF at 24-hrs, and robustly prevented the progression of tissue injury as detected by H&E and cresyl violet staining. Gene expressions of adhesion molecules (ICAM, VCAM, Selectins) in the brain were significantly increased in the TBI-group as compared to Sham at 24-hrs, and was downregulated in the RIPreC + TBI-group. Moreover, circulating endothelial progenitor cells (EPCs) and M2-type anti-inflammatory macrophage remained unchanged in TBI-group at 24-hrs but they were strongly upregulated in RIPreC + TBI-group. Circulating pro-inflammatory (M1-type) macrophage was significantly increased in the TBI-group as compared to Sham, which was downregulated in the RIPreC + TBI-group. RIPreC failed to improve CBF and prevent ischemic injury in AMPK$\alpha 1-/-$ mice. Genetic deletion of AMPKα1 also abolished the benefits of RIPreC in increasing EPCs and M2-type macrophage.

RIPreC is promising for the prevention of post-TBI injury and can be easily translated into subjects at high risk (soldiers and athletes). Since RIPreC increases circulating EPCs and M2-type macrophage, further studies are warranted for various RIC paradigms (Pre- and Post) in neurovascular protection and neurorestoration after TBI.

Key words
AMP-activated kinase, cerebral blood flow, remote ischemic conditioning, TBI

C2-31

MEMANTINE HYDROCHLORIDE AS A THERAPY FOR TRAUMATIC BRAIN INJURY: A PRECLINICAL STUDY USING THE CCI INJURY MODEL IN RATS

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Traumatic brain injury (TBI) results in glutamate release above physiological levels, which contributes to neuronal dysfunction. Memantine hydrochloride is a clinically well-tolerated moderate-affinity noncompetitive glutamate receptor antagonist with potential utility in TBI. We assessed the effects of memantine administration after controlled cortical impact (CCI) injury in adult rats, using a clinically-relevant dosing paradigm. Memantine (2.5, 5, 10 mg/kg) or vehicle was administered daily for 3 weeks starting 1 hr after CCI injury, by intraperitoneal injection during the first 4 days and thereafter per os over an additional 17 days. Measured histological variables included cortical tissue preservation, and cell number and synapse density in the hippocampus. Cerebral blood flow (CBF) was evaluated by arterial spin-label MR imaging. Behavioral testing included beam balance, beam walking, and Morris water maze tests. Hippocampal synapse density was preserved in rats treated with 10 mg/kg memantine. No differences were detected in cortical tissue preservation in memantine-treated groups compared to the vehicle-treated group. CBF deficits in the injured hemisphere were ameliorated by treatment with 10 mg/kg memantine. Rats treated with 10 mg/kg memantine recovered faster on the beam balance test, however no effects of treatment were observed in the beam walking test or the Morris water maze test. Collectively, these results demonstrate that in the adult rat CCI model, daily treatment with memantine over three weeks reduces cell and synapse loss and ameliorates CBF deficits. These data are consistent with reports of beneficial effects of memantine treatment in other brain injury paradigms including rat stroke models, and in patients with vascular dementia.

Key words
cerebral blood flow, controlled cortical impact, excitotoxicity, glutamate

C2-32

BLOCKING LYSOPHOSPHATIDIC ACID (LPA) INCREASES SUBVENTRICULAR ZONE PROLIFERATION BUT REDUCES EARLY NEUROBLAST MIGRATION AFTER TBI

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Lysophosphatidic acid (LPA) is a bioactive phospholipid that increases locally after injury. LPA can activate early injury responses such as excitotoxicity, inflammation, gliosis, and necrosis, and can inhibit neuronal differentiation and progenitor survival. It is unknown whether LPA effects adult neurogenesis after TBI. We have recently demonstrated that blocking the increase in LPA after controlled cortical impact injury in the mouse using a monoclonal antibody targeting the bioactive LPA (anti-LPA) improves behavioral outcome and SVZ neurogenesis. These data suggest reduction in LPA shortly after injury may improve behavioral outcome at least partly by inhibiting early neuroblast migration to the injured cortex. To test this hypothesis, anti-LPA antibody (25 mg/kg) or the isotype-matched control (n = 6/group) was administered intravenously to adult C57BL/6 mice, 2 hours after controlled cortical impact injury. The thymidine analogue CldU (50 mg/kg) was administered 3 times at 4 hour intervals starting 12 hours after the injury and euthanized at 3 days post injury. The brains were processed for standard double or triple-label immunohistochemistry to phenotype and then quantify populations of dividing cells within the subventricular zone (SVZ) and cortex using stereology. The results revealed a 2-fold increase in dividing neuroblasts (CldU+/DCX+) within the SVZ of injured anti-LPA-treated animals compared to the injured IgG-treated group ($P < 0.05$). Furthermore, there was a significant decrease in the total number of dividing cells within the cortex and in cortical neuroblast in the anti-LPA treated group compared to the injured controls ($P > 0.05$) These data suggest that blocking LPA shortly after injury delays or slows neuroblast migration from the SVZ to cortex. This would be consistent with overall lower cell death among progenitors and longer term improvement in recovery. Whether delayed cell migration and enhanced survival occurs is not known and is currently being tested. Support: R44NS087641-01

Key words
adult neurogenesis, lysophosphatidic acid, proliferation, SVZ

C2-33

DEGENERATION AND PROTECTION OF AXONAL SUB DOMAINS AFTER OPTIC NERVE CRUSH

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Myelinated axons are divided into several distinct domains, which includes the axon initial segment (AIS), nodes of Ranvier, paranodes, and juxtaparanodes. The AIS serves as both a physical barrier between the axonal and somato-dendritic compartments of the neuron and as the site of action potential (AP) initiation. Nodes of Ranvier are responsible for the rapid and efficient propagation of APs along the axon. Disruption of the AIS or nodes of Ranvier by genetic and/or pharmacological manipulation has a dramatic impact on the central nervous system. With this in mind, we have designed a series of experiments, which will allow us to assess the efficacy of neuroprotective paradigms upon axons of the central nervous system after insult. Using the optic nerve crush injury model, we have established a timeline for degenerative events of the nodes of Ranvier of the optic nerve and AIS of retinal ganglion cells. We have established that loss of nodes of Ranvier begins 6 hours after injury and progresses both distal and proximal to the injury site. A total loss of nodes of Ranvier occurs 1 week after injury and persists 1-month post crush. Loss of AIS in retinal ganglion cells begins 24 hours after injury and persists 1-month post crush. We have assessed the neuroprotective efficacy of MDL-28170 - a calpain inhibitor that has been shown to protect from AIS degeneration after ischemic injury. MDL-28170 spares nodes of Ranvier and AIS from degeneration 24 hours post injury.

Key words
axon initial segment, beta IV spectrin, nodes of Ranvier, optic nerve crush

C2-34

THE CYSTEINE PROTEASE CATHEPSIN B IS A KEY DRUG TARGET AND CYSTEINE PROTEASE INHIBITORS ARE POTENTIAL THERAPEUTICS FOR TBI

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Drug treatments for traumatic brain injury (TBI) may be developed by validation of new drug targets and demonstration that compounds directed to such targets are efficacious in TBI animal models using clinically relevant methods. The cysteine protease cathepsin B has been implicated in mediating TBI, but it has not been validated by gene knockout studies. This investigation evaluated mice with deletion of the cathepsin B gene receiving controlled cortical impact (CCI) TBI trauma. Results indicated that knockout of the cathepsin B gene resulted in amelioration of TBI shown by significant improvement in motor dysfunction, reduced brain lesion volume, greater neuronal density in brain, and lack of increased pro-apoptotic Bax levels. Notably, oral administration of the small molecule cysteine protease inhibitor E64d immediately after TBI resulted in recovery of TBI-mediated motor dysfunction, and reduced the increase in cathepsin B activity induced by TBI. The E64d outcomes were as effective as cathepsin B gene deletion for improving TBI. E64d treatment was effective even when administered 8 hours after injury, indicating a clinically plausible time period for acute therapeutic intervention. These data demonstrate that a cysteine protease inhibitor can be orally efficacious in a TBI animal model when administered at a clinically relevant time point post-trauma, and that E64d-mediated improvement of TBI is due primarily to inhibition of cathepsin B activity. Moreover, E64d has clinical potential because it has been safely used in man. These results validate cathepsin B as a new TBI therapeutic target.

Key words
cathepsin B, drug, target, TBI

C2-35

EFFICACY OF NEUROPROTECTIVE COMPOUND P7C3-S243 AFTER BLAST-MEDIATED TRAUMATIC BRAIN INJURY

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The prevalence of soldiers suffering from blast-mediated traumatic brain injury (TBI) has increased due to use of improvised explosive devices by enemy combatants. TBI results in progressive neuronal damage associated with chronic cognitive and neurological symptoms. Currently, there are no available pharmacotherapeutic interventions to prevent TBI induced neurological damage. Previously, we have demonstrated that P7C3-A20, a neuroprotective aminopropyl carbazole, protects rats from neurological deficit after fluid percussion injury. We have now evaluated the efficacy of P7C3-243, a more recently developed analog in the P7C3-series of neuroprotective compounds, after blast-mediated TBI in mice. When daily administration of P7C3-243 is initiated within 36 hr after TBI, mice are protected from deficits in the hippocampal-dependent Barnes maze task of learning and memory. This is associated with similar protection in electrophysiologic measures of synaptic transmission in the hippocampus (long term potentiation and paired pulse facilitation). We further reveal that blast-mediated TBI precipitates axonal degeneration in the absence of frank neuronal cell loss, and that P7C3-243 blocks this axonal loss. Our hope is that the chemical scaffold represented by P7C3-243 will provide a basis for developing new pharmacologic agents for patients with TBI.

Key word
therapeutic

C3-01

DELAYED MICROBLEEDS AND WHITE MATTER DAMAGE AFTER EXPERIMENTAL TRAUMATIC BRAIN INJURY

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This study evaluates microvascular abnormalities observed at acute and chronic stages following TBI in rats and examines pathological processes associated with these abnormalities. TBI in adult rats was induced by controlled cortical impact (CCI) of two magnitudes. Brain pathology was assessed in white matter of the corpus callosum for 24 h to 3 months following injury using immunohistochemistry (IHC). TBI resulted in focal microbleeds that were related to the magnitude of injury. At the lower magnitude of injury, microbleeds gradually increased over the 3 month duration of the study. IHC revealed TBI-induced focal abnormalities including brain barrier (BBB) damage (IgG), endothelial damage [Intercellular Adhesion Molecule 1 (ICAM-1)], activation of reactive microglia [Ionized calcium binding adaptor molecule 1 (Iba1)], gliosis [Glial Fibrillary Acidic Protein (GFAP)] and macrophage mediated inflammation [Cluster of Differentiation 68 (CD68)], all showing different temporal profiles. At chronic stages (up to 3 months), apparent myelin loss (Luxol fast blue) and scattered deposition of microbleeds were observed. Microbleeds were surrounded by glial scars and colocalized with CD68 and IgG puncta stainings, suggesting that localized BBB breakdown and inflammation were associated with vascular damage. Our results indicate that evolving white matter degeneration following experimental TBI is associated with significantly delayed microvascular damage and focal microbleeds that are temporally and regionally associated with development of punctate BBB breakdown and progressive inflammatory responses. Increased understanding of mechanisms underlying delayed microvascular damage following TBI could provide novel insights into chronic pathological responses to TBI and potential common mechanisms underlying TBI and neurodegenerative diseases.

Key words
BBB, CD 68, chronic TBI, GFAP, ICAM-1, microbleeds, microglia

C3-02

TRAUMATIC BRAIN INJURY-INDUCED MICRORNAS SUPPRESS PROSURVIVAL GENE EXPRESSION

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We and others have shown that TBI alters expression of several microRNAs (miRNAs) – small, non-coding RNAs that negatively regulate the expression of target genes involved in cell death/survival. Here we test the hypothesis that miR-15b, a TBI-induced miRNA suppresses the expression of prosurvival genes in dying neurons. Adult male Sprague-Dawley rats (350–400 g) were prepared for severe lateral fluid percussion brain injury, their brains removed 24 hours later, and total RNA containing microRNA isolated. We performed quantitative real-time PCR analysis (using TaqMan probes) of individual miRNAs in total RNA samples isolated from whole hippocampus and from laser capture microdissected samples of Fluoro-Jade-positive (dying) and Fluoro-Jade-negative (surviving) cells. To determine if dying neurons had higher levels of miR-15b, we performed *in situ* hybridization experiments using an Alexa 594 antibody to the digoxigenin-labeled locked nucleic acid (LNA) probe to miR-15b, and then stained the sections with Fluoro-Jade C. To confirm the negative regulation of BDNF, a predicted gene target of miR-15b, we cloned the sequence of the miR-15b binding site in the 3′ UTR of BDNF into the pmirGlo Dual Luciferase reporter vector, and performed the assay using a miR-15b mimic and antagomir. We have confirmed the up- and down regulation of several miRNAs in both whole rat hippocampi and individual dying and surviving neurons. miR-758, miR-379 and miR-181c were confirmed to be down regulated after TBI, and miR-18a and 19a were up-regulated in total RNA samples from whole hippocampi. We confirmed that dying FJ + neurons expressed higher levels of miR-15b than adjacent FJ- surviving neurons. miR-15b mimics reduced the expression of BDNF (reduced luciferase activity) and addition of LNA antagomir for miR-15b restored normal levels of luciferase activity, confirming that BDNF expression is negatively regulated by miR-15b. These studies are expected to aid in developing miRNA-based therapeutics that can be used to treat TBI.

Key word
miRNA

C3-03

ADENOSINE KINASE GENE ASSOCIATED WITH POST-TRAUMATIC EPILEPSY DEVELOPMENT

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Post-traumatic epilepsy (PTE) is a common complication following traumatic brain injury (TBI). Cell surface A_1 receptor activation by extracellular adenosine is a powerful endogenous anticonvulsant mechanism. We hypothesized that genetic variation within receptors, transporters or enzymes influencing the extracellular adenosine/A_1 receptor system would predict PTE risk. Previous work implicates genetic variation within the adenosine A1-receptor gene with PTE risk. Adenosine kinase (ADK) is up-regulated in astrocytes chronically after TBI and converts the endogenous intracellular anticonvulsant adenosine to inactive 5′-AMP. Ecto-5′-nucleotidase [(CD73); metabolizes extracellular 5′-AMP to adenosine, thereby increasing extracellular adenosine and lowering 5′-AMP)] and equilibrative nucleoside transporter type-1 [(ENT-1); allows equilibration of intracellular/extracellular adenosine concentrations]. 203 adult Caucasians without premorbid seizures and with moderate/severe TBI were recruited, and nine ADK tagging SNPs, three CD73 SNPs, and two ENT-1 SNPs genotyped. PTE was defined as seizures first occurring > 1wk post-TBI. Survival analyses were used to investigate time to first seizure and PTE risk while adjusting for time to mortality. Kaplan-Meier analysis revealed that TT (rs946185), AA (rs11001109), and GG (rs11001111) homozygosity within the ADK gene was associated with a shorter time to first seizure. Multivariate Cox Proportional Hazard analyses showed these genotypes were individually associated with increased PTE risk up to 3 yrs post-TBI, and a cumulative effect of each ADK variant on PTE risk (Hazard Ratio = 5.236; p = 0.012) was significant using an ADK gene risk score. This is the first clinical investigation on genetic variability within the ADK gene and epilepsy risk in any population. These results suggest that extracellular adenosine and/or intracellular 5-AMP may modulate biochemical mechanisms facilitating epileptogenesis and leading to PTE.

Support
NIH-R01HD048162; DODW81XWH-071-0701; NIHR01NR013342; NIH5P01NS030318

Key words
adenosine kinase, biomarker, genetic association studies, PTE, TBI

C3-04

DIFFERENTIAL REGULATION OF THE AKT SIGNALING PATHWAY IN RAT BRAIN AFTER PRIMARY BLAST INDUCED TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) has been a leading cause of morbidity and mortality in recent conflicts in Iraq and Afghanistan. However, the mechanisms of blast-induced TBI are not known. Akt, also known as Protein Kinase B (PKB), is a serine/threonine-specific protein kinase that plays a key role in neuroprotection and survival in the CNS. In the present study, the effect of a simulated single pulse primary blast wave on the levels of Akt and its downstream effector kinase, glycogen synthase kinase (GSK_{β}), in rat hippocampus and frontal cortex were investigated. Male Sprague-Dawley (SD) rats (350 – 400 g) were anaethetized in 3% isoflurane and stablized in a plastic sleeve for 8 min. The sleeve was then placed in the shock tube with the rat head positioned in the test area for shock wave exposure (25 psi). This system has been developed so that simulated single pulse ''primary blast'' exposure is accomplished with only minimal concussive and whiplash effects. After exposure, rats were closely observed for either 1 day or 7 days before being sacrificed. Phosphorylation of Akt and GSK was detected using their respective phosphorylated antibodies. Results showed that Akt and GSK phosphorylation were decreased or little changed 1 day after blast in the hippocampus and front cortex. However, p-Akt and p-GSK levels were dramatically increased 7 days after blast on the ipsilateral hippocampus, while p-GSK was also significantly increased on the contralateral hippocampus. Furthermore, p-Akt was increased on the contralateral cortex while p-GSK was increased on both sides of the frontal cortex. No significant changes in total protein levels of Akt and GSK were observed in both the hippocampus and front cortex. Because both Akt and GSK phosphorylation have been indicated in neuro-protection and neuro-damage, changes in the levels of Akt and GSK phosphorylation may contribute to neuropathology observed after primary blast exposure. Therapies targeting Akt and GSK phosphorylation pathways may help to protect the brain against blast-induced TBI.

Key words
Akt, GSK, primary blast, TBI

C3-05

ENDOGENOUS ELEVATION OF ACROLEIN FOLLOWING ACUTE TRAUMATIC BRAIN INJURY IN RATS

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Under healthy conditions, levels of reactive oxygen species are maintained to prevent the accumulation of damage by an endogenous antioxidant system, notably glutathione and vitamin E. In addition to the generation of free radicals, Acrolein is one of several reactive unsaturated aldehydes that are produced as a byproduct of lipid peroxidation during neuronal membrane damage. These aldehydes cause further bystander damage to biological macromolecules, phospholipids, and crosslink proteins, and result in the depletion of antioxidant reserves. Due to the relatively long activation of acrolein after lipid peroxidation, a therapeutic window exists to ameliorate cell damage caused by aldehydes. In this experiment hydralazine, a well-known scavenger of acrolein, was applied after traumatic brain injury (TBI) to reduce anatomical damage.

Sprague-Dawley rats were administered closed skull, weight drop TBIs. The treatment group received 5mg/kg hydralazine in saline injected intra-parenterally daily post-injury. A sham group received identical surgery injury group only omitting the weight drop.

The functional behavior of the rats were tested using a roto-rod and open field activity box after TBI. Forty-eight hours post-injury the brains were frozen, every tenth section collected for immunohistochemistry. Brain sections were for acrolein-lys protein adducts.

Acrolein fluorescence of injured rat brains was increased 80% over sham injuries and 40% more than hydralazine-treated animals. The relative luminosities of the acrolein-lys signal between the injury group (1.80) and the injury and treatment group (1.44) was statistically significant. We also examined specific brain regions for particular increases in acrolein staining.

Treatment with hydralazine at the dose used in this experiment did not significantly affect the blood pressure of the animals. The short post-injury window did not allow us to observe differences in the groups in the roto-rod and activity box tests. Future work will correct this.

This experiment demonstrated for the first time an increase in endogenous acrolein in brain tissue following experimental TBI and a decrease of brain damage after hydralazine treatment.

Key words
acrolein, closed injury, oxidative stress, reactive aldehydes

C3-06

MICRORNA DYSREGULATION OCCURS AT ACUTE TIME POINTS AFTER PENETRATING BALLISTIC-LIKE BRAIN INJURY

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Recent studies have shown that microRNAs (miRNAs), small RNAs that regulate cellular processes, may serve as novel markers of brain injury. Therefore five miRNAs, previously reported to change in the first 24 hours in other brain injury models, were examined as a proof-of-concept study in our severe TBI model. MicroRNAs were measured following penetrating ballistic-like brain injury (PBBI) where a temporary cavity was generated in rats disrupting 10% of brain volume. Sham animals received a craniotomy. Ipsilateral brain tissue was collected 4 h, 24 h, 72 h and 7 d post injury. Total RNA was isolated, reverse transcribed into cDNA and examined using real-time PCR with Taqman assays. The relative quantities of miRNAs were normalized to U6 endogenous reference gene. Similar to changes described in other TBI models, all miRNAs tested (miR-21, Let-7i, miR-124a, miR-146a, miR-107) were altered at 24 hours post PBBI. Let-7i demonstrated the most acute profile with a 1.6-fold increase at 4 h and a 2.7-fold increase at 24 h after injury. However, changes in Let-7i returned to normal by 72 h. MiR-146a demonstrated both an initial and delayed response to injury with a 2.4-fold increase 24 h after injury which resolved by 72 h but rebounded with a 3.9-fold increase at 7 days after injury. Most notably, miR-21 demonstrated an acute response with a 1.8-fold increase at 4 h that continued to increase over time where a 6.9-fold increase was measured by 7 days post injury. Initial pathway analysis indicated that these specific miRNAs are involved in regulating inflammation, cell migration and cell differentiation at 24 h, sterol metabolism at 72 h and matrix polymerization at 7 days. This study demonstrated that, similar to other TBI models, miRNAs are also altered by PBBI and exhibit temporal signatures of injury. Of interest, miR-21 showed sustained elevation for 7 days suggesting potential value as a therapy biomarker, and potentially aiding in our understanding of the chronic pathology following severe TBI.

Key words
severe TBI

C3-07

CONNECTING ACUTE NEUROTRAUMA TO CHRONIC TRAUMATIC ENCEPHALOPATHY: THE ROLE OF THE ENDOPLASMIC RETICULUM STRESS RESPONSE

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Chronic Traumatic Encephalopathy (CTE) is a progressive neurodegenerative disease characterized by neurofibrillary tau tangles. Blast-induced traumatic brain injury, the 'signature injury' of recent wars in Iraq and Afghanistan, and sport-related concussion are known risk factors for the development of CTE. The underlying mechanism linking acute neurotrauma to tau-dependent neurodegeneration is currently unknown. Endoplasmic reticulum (ER) stress has been implicated in several injury paradigms. We propose that the ER stress response is continually activated during CTE progression, and that manipulation of the pathway will improve behavioral outcomes and decrease tau hyperphosphorylation. We examined the contribution of the ER stress response on neural injury in young-adult male rats exposed to blast wave(s) as well as human CTE specimens using western blot analysis and immunohistochemistry (IHC). The three arms of the ER stress response were significantly elevated in the entorhinal cortex of human CTE brains with IHC: phospho-eukaryotic initiation factor 2 alpha (p-eIF2a) ($F(2,12) = 13.08$, $p < 0.01$), X-box binding protein ($F(2,12) = 38.55$, $p < 0.001$), and activation transcription factor 6 ($F(2,12) = 9.935$, $p < 0.01$). Additionally, inositol requiring enzyme 2 alpha, a marker of ER stress, was co-localized with hyperphosphorylated tau in both human CTE brains and repeat blast samples from Sprague Dawley rats 3 weeks post-injury. Caspase-12, a marker of apoptosis, was elevated at 24 h post-blast and was co-localized with C/EBP homology protein (CHOP), a protein activated by all arms of the ER stress pathway. The p-eIF2α phosphatase inhibitor, salubrinal, was used to significantly decrease CHOP ($F(2,15) = 9.172$, $p < 0.01$) on western blot, and also decrease impulsive behavior on elevated plus maze after blast injury ($F(2,12) = 4.409$, $p < 0.05$). Understanding how the ER stress response contributes to CTE development will improve diagnostic accuracy, and ultimately contribute to novel therapeutic targets for neurotrauma and neurodegenerative diseases.

Key words
blast traumatic brain injury, chronic traumatic encephalopathy, endoplasmic reticulum stress, tau-dependent neurodegeneration

C3-08

SPREADING DEPOLARIZATIONS MEDIATE GLUTAMATE EXCITOTOXICITY IN DEVELOPMENT OF ACUTE CORTICAL LESIONS

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Although glutamate excitotoxicity is presumed to play a pivotal role in secondary injury after TBI and stroke, failure of numerous clinical trials targeting NMDA receptors (NMDARs) suggests an incomplete understanding of the mechanisms involved in elevated glutamate after neurological injury. We hypothesized that cortical spreading depolarizations (CSD) are the mediator of excitotoxicity *in vivo*, since CSD exhibits significant overlap with excitotoxicity including glutamate release, reversal of excitatory amino acid transporters (EAATs), activation of NMDARs, and Ca^{2+} influx. Measuring extracellular glutamate in real-time with enzyme-based microelectrodes we found that CSDs evoked by 1 M KCl in uninjured cortex (duration 37.5 ± 2.5 s) produced synchronous elevations in glutamate (39.7 ± 2.4 s) (Pearson $r^2 = 0.51$, $p < 0.05$). Pharmacological inhibition of EAATs (TBOA) prolonged the duration of the glutamate signal (106.0 ± 19.9 s,

$p < 0.05$) and the CSD (93.0 ± 13.1 s, $p < 0.05$). A higher dose of TBOA induced CSDs even longer in duration (197.1 ± 25.1 s, $p < 0.05$) with a corresponding elongation in glutamate (188.1 ± 19.4 s, $p < 0.05$). These prolonged CSDs produced commensurate increases in lesion size after 24 h (235 ± 39 and 776 ± 61 Flouro-Jade$^+$ cells, resp., $p < 0.05$), while neither CSDs under control conditions nor glutamate injection caused significant neuronal death. Monitoring was performed during focal cerebral ischemia to determine the association of elevations in glutamate with CSDs in the natural evolution of lesion development. Here, glutamate never increased except during spontaneously occurring CSDs. Multiple types of CSDs were detected including anoxic terminal depolarizations (ischemic core) and prolonged transient CSDs (penumbra) (145.6 ± 19.7 s) that correlated with glutamate signal (112.0 ± 15.0 s) ($r^2 = 0.65$, $p < 0.05$). These results show 1) elevations in glutamate are directly related to CSD, 2) prolonged CSDs cause necrotic lesions, 3) excitotoxicity after ischemia occurs only during CSD. Since CSDs are observed abundantly in clinical TBI and stroke, monitoring this pathomechanism could selectively identify patients that may benefit from NMDAR antagonists.

Key words
cortical spreading depolarization, cortical spreading depression

C3-09

HIGH MOBILITY GROUP BOX-1 (HMGB1) EXPRESSION IN OLIGODENDROCYTES OF RATS SUBJECTED TO LATERAL FLUID PERCUSSION INJURY (LFPI)

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HMGB1 is nonhistone DNA-binding protein. Recently, cytoplasmic HMGB1 expression was reported to be associated with neuronal necrosis in traumatic brain injury (TBI). However, little information exists on HMGB1 expression in other CNS cell populations including the oligodendrocytes.

Male adult Sprague-Dawley rats were subjected to a 2.4 atmosphere LFPI. The animals were allowed to survive 10 min, 2 h, 6 h, and 24 h following injury (sham, n = 5; 10 min n = 8, 2 hrs n = 7, 6 hrs n = 7, 24 hrs n = 6). At the appropriate survival times, cerebrospinal fluid (CSF) and serum were sampled and the brain was prepared for immunohistochemical analysis. Brain sections were reacted with antibodies targeting HMGB1 and oligodendrocytes (CC-1) and/or beta amyloid precursor protein (APP). HMGB1 labeled sections were also analyzed by electron microscopy (EM).

In shams, HMGB1 was expressed in the nucleus of every cells including the oligodendrocytes. In paraventricular area of corpus callosum, cytoplasmic expression of HMGB1 was routinely observed in oligodendrocytes within 10 min and 2 h of injury. The number of cytoplasmic HMGB1-containing oligodendrocytes decreased with time. Cytoplasmic HMGB1-containing oligodendrocytes were located around APP-positive reactive axonal profiles, consistent with the finding of diffuse axonal injury. EM revealed necrotic change in all the oligodendrocytes revealing cytoplasmic HMGB1.

Collectively, our results support the premise that HMGB1 translocates from the oligodendrocyte nucleus to the cytoplasm as early as 10 min post injury and that such cytoplasmic HMGB1 is associated with oligodebdrocytic necrosis in the early phases of LFPI. Since these necrotic changes accompanied local axonal damage, we posit that these changes are associated with the onset of Wallerian degeneration.

This study is supported by NIH grants HD055813 and NS047463, and by MEXT KAKENHI Grant Number 24592737.

Key words
high mobility group box-1 (HMGB1), necrosis, oligodendrocyte, traumatic brain injury

C3-10

CORTICAL INJURY MODULATES THE PAIN PATHWAY PARTIALLY THROUGH INDUCIBLE NITRIC OXIDE SYNTHASE

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Headache is a highly prevalent symptom in all severities of traumatic brain injury (TBI) and is one of the most common symptoms of post-concussion syndrome. Post-traumatic headache (PTH) disorders may persist beyond the expected period of healing from inflammation after TBI. Despite being a common symptom of concussion, little is known about the pathogenesis of post-concussion headache. Release of the nociceptive neuropeptide, calcitonin gene-related peptide (CGRP) and nitric oxide within the pain pathway may contribute to chronic PTH, as found for migraine. Excessive release of nitric oxide (NO), a damaging and sensitizing free radical, is predominantly derived from the inducible nitric oxide synthase (iNOS) isoform after injury. Evidence suggests CGRP and iNOS/NO may have reciprocal interactions that facilitate a pain phenotype. Using a controlled cortical impact (CCI) model, changes in CGRP release and iNOS mRNA/protein levels in the trigeminal ganglia and trigeminal nucleus caudalis (TNC) were determined using ELISA, qRT-PCR, and immunohistochemistry. Pharmacological blockade and genetic modulation were also used to tease out the relationship between these two molecular targets. A rodent specific CGRP antagonist (MK8825; 100 mg/kg) or Sumatriptan (1 mg/kg) were administered to CCI mice to inhibit CGRP, while iNOS knockout mice were compared to wild-type mice with CCI. Headache-like behavior (von Frey mechanical allodynia) was characterized along with neurochemical pain correlates. iNOS mRNA and protein expression, as well as CGRP expression, were increased in the trigeminal ganglia and nucleus caudalis in CCI compared to controls, $p < 0.01$. CGRP and iNOS were co-localized in both the ganglia and brainstem. Inhibition of CGRP with an antagonist or sumatriptan significantly reduced the level of iNOS mRNA and protein, whereas genetic deletion of iNOS reduced the levels of CGRP. Significantly reduced mechanical von Frey thresholds indicate central sensitization after CCI. Findings confirm a reciprocal relationship between CGRP and iNOS exists and demonstrate their importance in pathological underpinnings of PTH.

Key words
headache, migraine, nitric oxide, post-concussion syndrome

C3-11

INCREASED INTRACRANIAL PRESSURE FOLLOWING CONTROLLED CORTICAL IMPACT EXACERBATES WHITE MATTER AXONAL INJURY AND ATROPHY

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Traumatic axonal injury is a major contributor to morbidity after severe traumatic brain injury (TBI). Reduction and avoidance of increases in intracranial pressure (ICP) continues to be the mainstays of treatment. It remains unclear whether elevations in ICP influence axonal injury.

Six week old male mice (C57BL/6J) were subjected to either controlled cortical impact (CCI) (N = 48) or sham surgery (SHAM, N = 12). Immediately after CCI, injured animals were randomized to a loose fitting plastic cap (OPEN) or replacement of the previously removed bone flap (CLOSED). Animals were sacrificed at 1 day, 7 days and 4 weeks post injury. Brain parenchymal ICP measurements were taken via a contralateral burr hole. Severity of white matter axonal injury was quantified utilizing stereological methods of beta amyloid precursor protein (B-APP) stained sections at 1 day and 7 days post injury.

Elevated ICP was observed in CLOSED animals 15 minutes and 1 day after injury compared to OPEN and SHAM (15 min 21.4 ± 4.2 vs. 12.3 ± 2.9 and 8.8 ± 1.8 mm Hg, $P < 0.0001$; 1 day 17.8 ± 3.7 vs. 10.6 ± 2.0 and 8.9 ± 1.9 mm Hg, $P < 0.0001$). Stereologic quantification of B-APP staining in the corpus callosum and ipsilateral external capsule revealed increased axonal swellings and bulbs in CLOSED compared to OPEN animals at 1 day (136 ± 24 vs. 94 ± 29 10^3 axons/mm^3, $P < 0.01$) and 7 days (99 ± 29 vs. 58 ± 15 10^3 axons/mm^3, $P < 0.001$) post injury. At 4 weeks post injury, CLOSED animals had increased white matter atrophy compared to OPEN and SHAM, resulting in smaller corpus callosum and external capsule volume (1.2 ± 0.1 vs. 1.5 ± 0.2 and 2.0 ± 0.1 mm^3, $P < 0.0001$).

Following controlled cortical impact, even moderate elevations in intracranial pressure were associated with increased axonal injury and white matter atrophy. Therapeutic interventions that ameliorate intracranial hypertension may influence white matter injury severity.

Key words
axonal injury, intracranial pressure, mouse, seconday injury

C3-12

IMPAIRED SYNAPTIC VESICLE DOCKING IS A NOVEL CONTRIBUTOR TO REDUCED NEUROTRANSMISSION AFTER TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) impairs neuronal function and can culminate in lasting cognitive impairment. While impaired acetylcholine release has been well established after experimental TBI, little is known about the mechanisms underlying this consequence. We hypothesized that alterations in synaptic vesicle distribution and reduced vesicular docking at the pre-synaptic membrane contribute to impaired neurotransmission. To examine the ultrastructural distribution of synaptic vesicles, Sprague-Dawley rats received 2.7 mm controlled cortical impact (CCI) or sham injury (n = 6/group) and the brains were processed for transmission electron microscopy at 1 week post-injury. In each animal, 20 randomly selected synaptic nerve terminals from the molecular layer of the hippocampus were imaged at 100 k magnification. Synaptic vesicle distribution was assessed by measuring the distance of each vesicle from the active zone for all terminals. CCI resulted in a significant reduction in vesicle frequency within 200 nm of the active zone ($p < 0.01$ compared to sham, repeated measures one-way ANOVA). Recent reports highlight that reduced vesicular density within 100nm of the active zone impairs vesicular docking and blunts neurotransmitter release. In a normal synapse, vesicular docking and neurotransmitter release requires formation of the SNARE complex. To examine the effect of TBI on the SNARE complex, rats received CCI or sham injury and were sacrificed at 6 hr, 1 d, 1, 2, or 4 weeks post-injury (n = 6/injury/time). Immunoblotting of unboiled hippocampal homogenates showed that SNARE complex formation, identified by SNAP-25 and syntaxin immunoreactivity, was reduced by at least 48% at 1 week ($p < 0.05$) and 2 weeks ($p < 0.01$) after CCI. Neurotransmitter release deficits have been well characterized at 1 and 2 weeks post-injury, suggesting that changes in synaptic vesicle docking contributes to impaired neurotransmission. In this study, we provide the first evidence that TBI alters synaptic vesicle distribution using quantitative ultrastructural analysis of electron micrographs. Our findings suggest that reductions in the standing pool of readily releasable vesicles and impaired SNARE complex formation are two novel mechanisms that contribute to the impaired neurotransmission after TBI.

Key words
electron microscopy, neurotransmission, synapse, vesicle

C3-13

SECONDARY MEMBRANE DAMAGE AND THE POTENTIAL FOR MEMBRANE-TARGETED NEUROPROTECTION

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Traumatic Brain Injuries (TBI) result in primary and secondary damage. The extended timescale of secondary injuries provides a larger window of opportunity for therapeutic interventions, but unfortunately there are currently no clinically successful pharmaceutical treatments for TBI. This indicates a need for a better understanding of the mechanisms and pathways of cellular degeneration and dysfunction after injury in order to better develop effective therapeutic interventions for patients with TBI. Plasma membrane damage, calcium influx, mitochondrial damage, and increased oxidative stress have all been identified as key players in the TBI pathway. Membrane damage has been hypothesized to be an initiating factor in the secondary damage pathway and previous studies have shown that sealing the damage using Poloxamer 188(P188) is neuroprotective after mechanical shear stress injury. However, the therapeutic potential of P188 and targeted membrane protection is limited if membrane damage is only occurring at the beginning of the secondary damage pathway. The results here make the case that secondary membrane damage is occurring and that it can be targeted using P188. Aspects of the injury pathway downstream of initial membrane damage were targeted and induced using Calcium Ionophore A23187 to increase intracellular calcium without general membrane damage, CCCP to damage mitochondria, and the hydroperoxide donor tert-butyl hydroperoxide to increase oxidative stress. These treatments were used to create isolated perturbations of pieces of the TBI pathway in cultured chick forebrain neurons. Axonal injury was quantified by normalizing the number of focal swellings (beads) by the length of the axon. P188 used in combination with each of these resulted in a statistically significant reduction in beading. Membrane permeability was quantified by measuring the loss of intracellular Calcein Red/Orange. Together, these results provide evidence for the presence of secondary membrane damage and the possibility of targeted membrane sealing as a therapeutic tool for treating TBI.

Key words
calcium, membrane damage, membrane protection, mitochondria, oxidative stress, poloxamer 188

C3-14

REGIONAL AND TEMPORAL HISTOPATHOLOGICAL CHANGES FOLLOWING MILD CONCUSSIVE BRAIN INJURY

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The purpose of this study was to identify histopathological changes across brain regions of interest in the WRAIR projectile concussive impact (PCI) model. Rats were subjected to single PCI targeted at the right temporoparietal region. Sham control group received anesthesia only. All animals were then sacrificed by transcardial perfusion at 6 h, 24 h, 72 h and 7 d post-injury (n = 6/group/time point). A separate group of rats subjected to repeated PCI (4xPCI, 1 h-interval; n = 6) were sacrificed at 6 h following the first impact. Series of coronal brain sections (40 μm) were immunostained for β-APP, GFAP and Iba-1. Positive-stained areas were quantified using threshold analysis in cortical and subcortical regions. A single PCI injury produced significant bilateral increases in accumulation of β-APP with bulb formation indicative of axonal injury that was primarily evident in the corpus callosum ($p < .05$ vs. sham). The increase peaked at 6 h post-injury and resolved by 72 h. Repeated PCI caused a significant increase (3-fold vs. single PCI $p < .05$) in β-APP accumulation near the impact location at 6 h. Hippocampal GFAP levels were slightly up-regulated at 6 h following a single PCI and were significantly higher than sham at 24 h in both hemispheres, suggestive of astrocyte activation. GFAP expression was still elevated at 7 days, but no longer significantly higher than sham control. Repeated PCI significantly increased GFAP expression at 6 h post-injury ($p < .05$ vs. single $PCI_{6\ h}$ or sham). Significant microglial activation, indicated by Iba-1, was detected at 6 h and 72 h in the hippocampus following a single PCI (vs. sham) and then resolved at 7 d post-injury. Iba-1 levels following repeated PCI group were significantly (2-fold) higher than those detected after a single PCI at 6 h post-injury. Overall, these findings demonstrated that a single PCI is capable of producing quantifiable axonal injury and glial activation in the absence of any gross pathology. Further, the profiles of these neuropathological changes are time-dependent and region-specific and are sensitive to the cumulative effects of repeated concussive impact.

Key words
axonal injury, concussion, glial activation, histopathology

C3-15

REGION-SPECIFIC IMPAIRMENT OF CEREBRAL MITOCHONDRIAL BIOENERGETICS FOLLOWING PENETRATING BALLISTIC-LIKE BRAIN INJURY IN RATS

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Mitochondria play a pivotal role in secondary brain damage mechanisms following traumatic brain injury (TBI), which have positioned themselves as leading target for therapeutic intervention. This study was designed to assess regional cerebral mitochondrial bioenergetics following penetrating ballistic-like brain injury (PBBI). Sprague-Dawley rats received either sham injury (craniotomy; n = 11) or unilateral frontal PBBI (10% injury severity; n = 15). Rats were euthanized at 2 hr post-injury, and brain regions of interest were dissected and processed for mitochondrial Ficoll isolation. The Seahorse Bioscience XF^e24 Flux Analyzer was used to evaluate mitochondrial bioenergetics. Outcome metrics include mitochondrial oxygen consumptions during: ADP/pyruvate/malate-induced complex-I respiration (State III), oligomycin-induced minimal complex-I respiration (State IV), uncoupler (2,4-dinitrophenol)-stimulated maximal complex-I respiration (State V-I), and succinate/rotenone-induced complex-II respiration (State V-II). Regional differences intrinsic to cortex, striatum and hippocampus were compared in the uninjured brains (sham control). The results show that cortex exhibited significantly higher State III respiration compared to striatum and hippocampus ($p < 0.05$). Additionally, hippocampus showed lower State IV ($p < 0.05$) and State V-I respiration ($p = 0.07$) compared to cortex and striatum, indicative of a differential profile of basal mitochondrial function across normal (sham) brain regions. Subsequently, the region-specific response to PBBI was compared to sham controls. No between-group differences were detected in complex-I function measured by State III and State IV respiration across all regions tested. However, complex-I maximal respiration measured by State V-I respiration was significantly reduced in cortex (34%; $p < 0.05$ vs. sham) and striatum (51%; $p < 0.05$ vs. sham), but not hippocampus, demonstrating an acute (2 hr post-injury) onset of bioenergetic failure in cortex and striatum following PBBI. No differences were detected in State V-II respiration, which suggests complex-II function was not compromised at this time point post-PBBI. Overall, the results indicate that PBBI produced region-specific mitochondrial bioenergetic deficits that are unique to the penetrating, temporary cavity mechanism. Furthermore, the results demonstrate an acute onset of PBBI-induced mitochondrial dysfunction which underscores the importance of early therapeutic intervention targeting mitochondrial bioenergetics for neuroprotection.

Key words
mitochondrial bioenergetics, penetrating ballistic-like brain injury, respiration

C3-16

THE INFLAMMASOME IS ACTIVATED IN THE CORTEX OF RATS FOLLOWING PENETRATING BALLISTIC BRAIN INJURY

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Penetrating traumatic brain injury (PTBI) remains a significant cause of death and disability in the United States. A rodent model of PTBI known as penetrating ballistic-like brain injury (PBBI) has helped uncover several pathophysiological mechanisms associated with PTBI, including reduced glucose uptake followed by neurodegeneration. It is known that activators of innate immunity contribute to glycolysis failure. Here, we aim to characterize proinflammatory cell death (pyroptosis) mediated by the inflammasome (a multiprotein complex, composed of apoptosis-associated speck-like protein containing a CARD (ASC) and caspase-1) in PBBI. In this study, male Sprague-Dawley rats (280–350 g) were subjected to PBBI. Protein lysates from sham animals (n = 3) and animals that were injured and sacrificed at different time points (4 h, 24 h, 48 h, 72 h, and 1 week) (n = 3-5) were analyzed by immunoblotting using anti-IL-1β, anti-caspase-1, anti-ASC antibodies. Our data indicate that caspase-1 and ASC expression in the ipsilateral cortex were significantly increased

at 24 h and 48 h after injury compared to sham while IL-1β expression was significantly increased at 48 h, 72 h, and 1 week after injury compared to sham. Moreover, partial purification of the pyroptosome indicated by ASC laddering in the ipsilateral cortex suggests activation of pyroptosis. In summary, this is the first report of inflammasome activation in PBBI and suggests that pyroptosis occurs in conjunction with previously characterized cell death mechanisms such as apoptosis, thus leading to ipsilateral cortex tissue loss. Whether, pyroptosis plays a more relevant role than apoptosis after PTBI is under investigation.

Key words
ballistic-like, brain injury, penetrating, traumatic

C3-17

DISTRIBUTION OF MICROGLIAL MORPHOLOGIES SHIFT WITH THE BLOCKADE OF NOGO-66 RECEPTOR

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Diffuse traumatic brain injury (TBI) initiates secondary pathology, including inflammation and dysmyelination. Considering these pathologies, activated microglia would migrate through fields of growth-inhibitory myelin byproduct, Nogo. We hypothesized that the Nogo-66 receptor antagonist peptide NEP(1-40) would shift distributions of microglia morphologies based on the environment permissiveness.

Adult male rats were subjected to midline fluid percussion sham- or brain-injury. Animals received vehicle or drug (NEP(1-40), i.p., 15 min and 19 h) and brains were collected at 2 h, 6 h, 1 d, 2 d and 7 d. Immunohistochemistry for myelin (MBP; myelin basic protein and CNPase), microglia morphology (Iba-1; ionized calcium binding adapter protein), and Nogo was analyzed in sensory cortex.

Pronounced dysmyelination was evident at 1 d post-injury, as evidenced by decreased MBP and CNPase staining, as well as loss of white matter organization, compared to sham. Ramified microglia were predominant in sham-injured cortex at all time points. Injury shifted microglial morphology from ramified to activated as early as 2 h post-injury, regardless of treatment. NEP(1-40) administration further shifted distributions of microglial morphologies to increased rod morphology compared to vehicle-treated. Moreover, NEP(1-40) increased proportions of macrophages from 2 h to 2 d post-injury. By 7 d post-injury, no differences in the distributions of microglia were noted between vehicle and NEP(1-40).

This study begins to link white matter and inflammatory pathologies after diffuse TBI. NEP(1-40) treatment shifted the distributions of microglia morphologies, with an early increase in rod morphology. The role of rod microglia is unknown, however, rods may provide early stabilization to damaged neurons enabling restoration of circuits. Therefore, the interaction between myelin-associated proteins and microglia remains intriguing and encourages further investigation into neuronal circuits and behavioral morbidities.

Supported, in part, by NIH NINDS R01NS065052 and PCH Mission Support Funds.

Key words
diffuse brain injury, microglia, nogo

C3-18

TIME COURSE OF MICROGLIA/MACROPHAGE ACTIVATION AFTER TRAUMATIC BRAIN INJURY IN MICE

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A major factor in the long-term outcome after Traumatic Brain Injury (TBI) is a delayed, secondary inflammatory response within the CNS, which is primarily mediated by microglia. In addition, there is infiltration of peripheral macrophages. Microglia/macrophages can be classified as *non-activated* (anti-inflammatory), *activated* (pro-inflammatory), or *slightly activated* (those with morphologies in between). TBI causes an increase in the activated microglia/macrophages population and ratio of activated:non-activated within the brain. We hypothesized that this change occurs between 24 and 72 hours after injury and investigated differences between resident microglia and infiltrating macrophages.

We used a Controlled Cortical Impact (CCI) device to administer a unilateral injury to the temporal lobe of mice. Microglia/macrophages were evaluated via immunohistochemistry using Iba1, a marker for microglia/macrophages, and CD11c, a marker for myeloid dendritic cells. Activation status was based on morphology of Iba1$^+$ cells.

We observed an increase in the number and ratio of activated: non-activated microglia/macrophages in the hippocampus at 72 hours in comparison to both the 24 hour and uninjured brains. At 24 and 72 hours, we observed marked co-labeling with Iba1 and CD11c. In addition, we observed significant, chronic activation of microglia/macrophages specifically in the ipsilateral thalamus at 28 days.

Our experiments demonstrated a dramatic increase in the activated microglia/macrophage population within the hippocampus between 24 and 72 hours after initial injury, a decrease by 28 days, and chronic activation in the ipsilateral thalamus at 28 days. However, we could not definitively discern resident microglia from infiltrating macrophages using CD11c.

Key words
hippocampus, IBA1, microglia, thalamus

C3-19

SNTF IMMUNOHISTOCHEMISTRY IDENTIFIES A PREVIOUSLY UNDETECTED POPULATION OF DEGENERATING AXONS FOLLOWING TRAUMATIC BRAIN INJURY

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Up to 15% of patients with mild traumatic brain injury (mTBI) or ''concussion'' develop persistent, debilitating symptoms. While the pathology of mTBI is largely unknown, diffuse axonal injury (DAI) may be an important consequence of injury. A recent study indicates that blood measurements of the calpain-cleaved alpha-II Spectrin N-terminal fragment (SNTF) may be useful not only for the diagnosis of mTBI, but in identifying patients that will have persisting neurocognitive dysfunction. Here we examined the pathological basis of increased serum-SNTF using both post-mortem cases of human TBI, as well as a unique swine model of head rotational acceleration injury (RAI) that induces DAI.

Miniature swine were subjected to the RAI model of TBI and compared to shams. IHC was performed specific for SNTF, as well as the amyloid precursor protein (APP), the current gold-standard for identifying axonal pathology. Double fluorescent labelling was performed to determine co-localization. In parallel, IHC was performed on cases of single human TBI (survival < 7 d; n = 17) versus age-matched controls (n = 16) from the Glasgow TBI Archive.

Following both swine RAI and human TBI, SNTF reactive axons were observed acutely (6 h) and up to 3 days post-injury. SNTF positive axons appeared as multiple accumulations like ''beads on a string'', potentially indicating degeneration. However, these axons were of relatively normal diameter versus the greatly swollen APP-reactive axons indicative of transport interruption. Interestingly, even at 3 days post injury, there was a distinct subset of SNTF axons that were APP negative.

Here we show that SNTF mTBI biomarker findings have a biologically plausible pathological correlate. Moreover, SNTF IHC may elucidate a previously unidentified subpopulation of injured axons undergoing degeneration by a novel mechanism independent of transport interruption. This observation may identify an important therapeutic target in TBI, as well as a novel approach to the comprehensive neuropathological analyses of DAI.

Key words
alpha-II spectrin N-terminal fragment, diffuse axonal injury, mild TBI, rotational acceleration

C3-20

TOLL-LIKE RECEPTOR 4 MEDIATES POST-TRAUMATIC CHANGES TO THE CIRCADIAN CLOCK

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Traumatic brain injury (TBI) is a leading cause of death and disability. About 2% of the population currently lives with the long-term consequences of TBI. In particular, 46% of patients are diagnosed with depression in the 12 months following injury, making it the most commonly diagnosed neuropsychological illness after TBI. Despite the high comorbidity between TBI and depression, the relationship between them remains unclear. Circadian rhythms are disrupted in TBI patients and have been implicated in the pathology of depression. These rhythms are created by oscillating molecular patterns and are particularly susceptible to immune activation, such that occurs after TBI. Previous work from our lab shows that the innate immune receptor, Toll-like receptor 4 (TLR4) is activated after TBI and inhibition of TLR4 reduced neuroinflammation and secondary injury. We hypothesize that activation of TLR4 after TBI disrupts the molecular clock and contributes to depressive behavior. Using a mouse model of TBI, we found that gene expression patterns of multiple components of the molecular clock are decreased 72 hours after injury. This disruption is temporally correlated with increased depressive phenotype, as assessed by the open field test and tail suspension test. TLR4 knockout animals do not exhibit post-traumatic gene changes in molecular clock components and have an attenuated depressive phenotype. These data indicate that circadian changes after TBI are mediated at least in part by TLR4 activation and may contribute to depressive phenotypes.

Key words
circadian, inflammation, microglia, neurobehavioral outcomes

C3-21

APOE INFLUENCE ON DENDRITIC SPINE LEVELS FOLLOWING MILD TRAUMATIC BRAIN INJURY

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Dendritic spine loss is an early consequence of traumatic brain injury (TBI). Spine loss could potentially explain why patients report a variety of symptoms after injury. Genetic predisposition has also been shown to influence severity and recovery following TBI. The apoE4 allele is synonymous with poorer recovery and death after TBI; the incidence of this gene is increased in those who suffer from Chronic Traumatic Encephalopathy (CTE); and a growing number of studies have associated the detrimental effects of apoE4 with facilitating a more pro-inflammatory state in the brain. The mechanism by which apoE isoforms differentially influence recovery and inflammatory status is not well understood. Here, we wanted to determine the role of APOE genotype on dendritic spine levels and inflammation, following single and repeat mTBI. We administered a midline, close-head impact to adult APOE3 and APOE4 targeted-replacement (TR) mice and visualized neurons and dendritic spines 24 h post injury using Golgi stain. All mice present with no evidence of cell loss or neuroinflammation after a single mTBI; however mTBI caused a 12.4% decrease in dendritic spine number on apical oblique (AO) dendrites in layer II/III of injured APOE3 mice. In contrast, mTBI caused a 15.4% increase in dendritic spine number on AO dendrites in layer II/III of injured APOE4 mice. After repeat mTBI (single injury, 30 days), spine levels returned to baseline in injured APOE3 mice, however spine levels remained elevated in injured APOE4 mice. We also found that injured APOE3 mice had an average reflex return time of 105s following single and repeat mTBI. Interestingly, injured APOE4 mice had an average reflex return time of 71s after single mTBI, yet following repeat mTBI, average reflex return time wasn't significantly different from sham APOE4 mice (51s). Injured APOE4 mice displayed more white matter inflammation and damage of the optic tract, compared to injured APOE3 mice, which persisted up to two months following the final impact. Here, our findings demonstrate that APOE genotype differentially influences dendritic spine levels, reflex return time, and promote a pro-inflammatory state in the brain following mTBI.

Key words
ApoE genotype, dendritic spines, repeat mTBI

C3-22

ALTERED NEUROGENESIS FOLLOWING A FLUID PERCUSSION INJURY IN MICE

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Neurogenesis persists in the hippocampus and subventricular zone throughout the lifespan of rodents. Neurons born in the subventricular zone migrate via the rostral migratory stream (RMS), primarily to the olfactory bulbs, and to other olfactory structures. In the hippocampus, progenitor cells in the sub-granular zone give rise to newborn granule cells that can become functionally integrated into the granule cell

circuitry. Newly-born granule cells undergo a relatively stereotypical development, where they remain closely association with the GFAP-expressing, radial glial-like progenitor-cell mothers. These radial glial-like cells provide a scaffold for the newborn neurons to integrate into the existing granule cell circuitry. Previous studies have demonstrated that alterations to this relationship promote a pro-epileptogenic, recurrent excitatory circuitry. Thus, for the current study, we examined neurogenesis in the hippocampus of mice that received a fluid percussion traumatic brain injury (TBI) that was previously shown to result in increased seizure susceptibility. The results show an increase in hippocampal neurogenesis between 1 and 7 days after TBI. In addition, after TBI, newborn granule cells exhibited hilar basal dendrite sprouting, an anatomical hallmark of recurrent excitatory circuit formation. Moreover, the hilar basal dendrites were observed to grow along an ectopic glial scaffold. Finally, examination of neurogenesis within the RMS also revealed a TBI-induced increase in cell proliferation along this pathway. Future studies are needed to determine the functional significance of these TBI-induced neurogenic alterations.

Key words
basal dendrites, hilar basal dendrites, hippocampus, neurogenesis, rostral migratory stream, subventricular zone

C3-23

EFFECT OF TRAUMATIC BRAIN INJURY ON WILD-TYPE ALPHA-SYNUCLEIN EXPRESSION IN RAT HIPPOCAMPUS

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Synucleins (Syn), a family of synaptic proteins, includes alpha-synuclein (α-Syn), which plays a pivotal role in Parkinson's disease and related 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. Thus, the goal of the project was to examine the effects of TBI produced on wild-type α-Syn expression at 6 hours to 8 weeks post injury. Male Sprague-Dawley rats were anesthetized and surgically prepared for controlled cortical impact (CCI) injury (4 m/sec, 2.6 mm) or sham surgery. Rats were randomly assigned TBI or sham surgery and sacrificed for Western blot analysis and immunofluorescence double labeling assay by using commercial available antibodies. Semiquantitative measurements of the hippocampal tissues from rats sacrificed at 6 hour, 1 day, 1 week, 2 weeks, 4 weeks, and 8 weeks after injury or sham operation ($N = 6$ per group per time point) that were assessed using Western blot analysis show that expression of α-Syn are decreased ipsilaterally from 6 h to 8 weeks in the hippocampus ($P < 0.05$). Double-label immunofluorescent staining sacrificed at 1 week after TBI or sham for α-Syn, neuron marker NeuN and astrocytes marker glial fibrillary acidic protein (GFAP) confirmed the Western blot findings. The increased expression of GFAP represents concomitant astrogliosis. This study suggests that wild-type α-Syn protein in the ipsilateral hippocampus is decreased after TBI compared to the sham controls. 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. Support: Veterans Administration, the Pittsburgh Foundation, NIH-NS40125, NIH-NS060672.

Key words
alpha-synuclein, immunofluorescence, traumatic brain injury, Western blot

C3-24

AUGMENTED FEAR BEHAVIOR FOLLOWING TRAUMATIC BRAIN INJURY IS ACCOMPANIED BY INCREASED CORTICAL GABA

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Individuals with mild traumatic brain injury (mTBI) often develop changes in affect including anxiety, depression, or symptoms resembling posttraumatic stress disorder (PTSD). It is unclear how mTBI results in PTSD-like symptoms, although studies suggest decreased prefrontal cortex (PFC) activation alters responses in downstream regions associated with fear learning, such as amygdala and hippocampus. To investigate this, we used a mouse model of mTBI and examined the effects of mild injury on fear behaviors and associated neurochemical alterations in the PFC.

Anesthetized male C57BL/6 mice (10–12 wks) impacted over the sagittal suture of the intact skull or exposed to surgery alone (sham controls). To assess levels of excitatory and inhibitory neurochemicals, PFC was harvested for proton magnetic resonance spectroscopy analysis *ex vivo* at 11.7 T at 8 d post-injury. A second cohort was used to assess fear response (freezing) to contextual fear conditioning (FC) at 14 d post-injury. FC consisted of 5 phases: habituation, acquisition, extinction, reinstatement, and extinction recall of conditioned fear.

Mice with mTBI demonstrated significantly increased freezing during acquisition and extinction compared to controls. No differences in baseline freezing or freezing during reinstatement or extinction recall after reinstatement. GABA levels were significantly increased in the PFC of mTBI mice compared to controls.

The increased acquisition and slower extinction of conditioned fear observed in mTBI mice resemble features of FC reported in PTSD and mTBI patients. Increased GABA in the PFC may reflect an increase in inhibitory activity and support the hypothesis that mTBI-induced PFC hypoactivity limits top-down control over subcortical areas involved in FC; thereby increasing susceptibility to affective disorders. Therefore, this model of mTBI-induced changes in PFC may give valuable insight into mechanisms involved in developing affective alterations following mTBI.

Key words
affective disorders, animal model, neuroplasticity, traumatic brain injury

C3-25

ASTROCYTE-MEDIATED CIRCUIT REORGANIZATION: EVIDENCE FROM SYNAPTOGENIC EXPRESSION AFTER EXPERIMENTAL DIFFUSE TRAUMATIC BRAIN INJURY

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Synaptogenesis is fundamental to the study of neuronal circuit reorganization after diffuse traumatic brain injury (TBI), which depends on astrocyte-secreted thrombospondins (TSP), glypicans (Gpc), and hevin. These molecules have not been assessed in the context of TBI. By investigating synaptogenic expression over time post-injury, we can delineate synaptogenic events responsible for circuit reorganization and their contribution to functional and behavioral change. We hypothesize that TBI will change expression of astrocyte-secreted synaptogenic molecules over a time course that may influence circuit reorganization in the ventral posteromedial (VPM) thalamic nucleus. In these experiments, male Sprague-Dawley rats (330–350 g) underwent sham or moderate midline fluid percussion brain injury (mFPI; 1.9 atm; 6–10 min righting reflex). At multiple times points over 8 weeks post-injury, gene expression and protein levels of astrocyte-secreted mediators of synaptogenesis were quantified from VPM tissue biopsies. TSP1 gene expression was increased significantly at 1 d and 5 d post-TBI in comparison to sham ($p < 0.05$). $\alpha 2\delta 1$, the receptor for TSP, exhibited a significant decrease in gene expression at 3 d and 9 d post-injury compared to sham ($p < 0.05$). Gpc4 exhibited a significant decrease at 7 d, 14 d, and 28 d compared to 1d post-TBI ($p < 0.05$). Hevin exhibited a sustained injury-dependent decrease in gene expression from 2 d-7 d post-TBI compared to sham ($p < 0.05$). Corresponding protein level quantification is ongoing. Here we determined a temporal profile of astrocyte-secreted synaptogenic gene expression in the VPM after diffuse TBI that implicates astrocyte-secreted molecules in circuit reorganization. Increased gene expression for TSP1 in the first week post-injury, in synchrony with prolonged decreased expression of other astrocyte-secreted mediators of synaptogenesis, supports a role for TSP1 as a primary mediator of synaptogenesis after diffuse TBI. Prolonged decreased expression of synaptogenic molecules after TBI implicates that mechanical forces initiate a disease process, rather than an event.

Supported, in part by NIH R03 NS077098, NIH R01 NS065052, and PCH Mission Support

Key words
astrocyte, circuit reorganization, diffuse brain injury, thrombospondin

C3-26

MORPHOLOGICAL REORGANIZATION OF THALAMIC NEURONS AFTER DIFFUSE TBI MAY UNDERLIE ATTENUATED IMMEDIATE EARLY GENE ACTIVATION

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Diffuse traumatic brain injury (dTBI) causes late-onset, chronic sensory sensitivity to whisker stimulation by 28 days post-injury (DPI) after moderate midline fluid percussion injury (FPI). We hypothesize that late-onset sensory sensitivity results from maladaptive circuit reorganization within the thalamic relay of the whisker-barrel circuit associated with changes in neuron morphology detected by impaired circuit activation. Adult male, Sprague Dawley rats underwent moderate midline FPI (1.9 atm, 6–10 min righting reflex) or sham control procedures. Neuron morphology was quantified in the somatosensory thalamus at 1, 7, 28 and 56 DPI ($n = 4$/time point) in Golgi stained tissue using MicroBrightField Neurolucida software. Circuit activation at 28 DPI was evaluated by immediate early gene (IEG) expression of ARC and EGR3 in the thalamus following whisker stimulation at several time points ($n = 4$-5) using qPCR. Golgi-stained neuron morphology revealed a significant decrease in the number of branch points, ends and mean process length at 7DPI in comparison to sham ($p < 0.05$). At 28 DPI, these parameters were similar to sham. Sholl analysis indicated the greatest changes between 30–70μm from the soma. Whisker stimulation-induced IEG ARC expression was significantly decreased in injured animals at 15 and 30 minutes post-stimulation compared to sham ($p < 0.05$). There was no whisker stimulation or injury effect on EGR3 gene expression. Thus, thalamic neurons were truncated early, but returned towards uninjured sham shape by 28 DPI; a time course paralleling sensory sensitivity after diffuse TBI. Attenuated circuit activation (ARC) at 28 DPI supported structural reorganization underlying impaired circuit function in the latter phases of TBI. These outcome measures may be critical in evaluating therapeutic approaches to circuit restructuring.

Funding: NIH R03-NS077098, NIH R01-NS065052, Phoenix Children's Hospital Mission Support

Key words
circuit reorganization

C3-27

STIMULATION OF THE MEDIAL SEPTUM DRIVES HIPPOCAMPAL THETA OSCILLATIONS LEADING TO PERSISTENT INCREASES IN THETA PHASE COHERENCE

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Traumatic Brain Injury (TBI) attenuates hippocampal theta oscillations and is associated with poor episodic memory retrieval in rodents. Previously, we demonstrated that 7.7 Hz theta stimulation of the medial septal nucleus (MSN) for 1 minute prior to training in the Barnes Maze task improved spatial learning in TBI injured rats. We now hypothesize that minimizing the duration of stimulation to entrain oscillations will allow for more physiological oscillatory patterns and ultimately improve cognitive function. Sprague-Dawley rats (300–350 g) underwent a lateral fluid percussion TBI (2.12-2.15 atm), and were immediately implanted with three twisted bipolar electrodes: MSN, ipsilateral hippocampus and ipsilateral medial pre-frontal cortex (mPFC). Animals were tested four times on an object exploration behavioral task and were randomly assigned to receive each of 0, 15, 30, or 60 seconds of pre-stimulation over these four trials. Theta oscillation analysis included examining the percentage of time spent oscillating in theta at each electrode and also the phase coherence of theta between electrodes. Oscillations were evaluated 1 minute prior to stimulation, during stimulation, and for 15 minutes during the behavioral task. During stimulation, coherence between mPFC-hippocampus increased in a time-of-stimulation-dependent manner. Stimulation also improved the percentage of time spent oscillating in theta in both the mPFC and hippocampus. In addition, following 30 or

60 seconds of stimulation there was a persistent increase in phase coherence between the MSN-mPFC and MSN-hippocampus lasting the duration of the behavioral trial. We now demonstrate that there is a time-of-stimulation dependent increase in theta phase coherence across distal nodes of the learning circuit both during stimulation and persisting for 15 minutes following stimulation. The goal of these preclinical trials is to optimize stimulation paradigms to entrain physiological theta and restore cognitive function. These data provide further support that neuromodulation represents an exciting approach for improving outcome following TBI.

Key words
deep brain stimulation, neuromodulation, theta oscillations, traumatic brain injury

C3-28

DECREASED HEMISPHERIC SWELLING FOLLOWING TBI IN MICE LACKING TREM2

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The consequences of traumatic brain injury (TBI) vary by individual, but can include long-term neurological deficits and increased risk of Alzheimer's disease. It is difficult to predict which individuals will develop unwanted TBI associated sequelae. Microglia are brain resident macrophages and ''first responders'' to changes in CNS function. Following neuronal injury, cell death and/or amyloid pathology, microglia rapidly increase expression of the orphan immune-modulatory receptor, Triggering Receptor on Myeloid cells-2 (TREM2). Microglial expression of TREM2 is also increased during systemic inflammation even without blood-brain-barrier disruption. Individuals lacking a functional TREM2 reveal the importance of TREM2 for brain function. Absence of a functional TREM2 causes early onset cognitive dementia while expression of a TREM2 allele with a mutation in the putative ligand-binding domain correlates with a 3-fold higher risk of Alzheimer's disease. We hypothesized that inflammatory status and level of TREM2 expression at the time of TBI would alter the evolution of TBI pathology. Therefore, we contrasted lesion size, hemispheric swelling and microglial activation 7 days post-moderate controlled cortical impact (CCI) in wild-type (WT) mice without systemic inflammation, in WT mice with LPS systemic challenge 24-hrs before CCI and in TREM2KO mice. Surprisingly, we found decreased hemispheric swelling following TBI in both TREM2KO and LPS challenged WT mice, which exhibit elevated microglial TREM2 expression. There were no significant differences between lesion size and blood deposition between the three conditions as detected by MRI, qPCR and nanostring analysis of gene expression within the impacted cortex and in purified microglia revealed that both TREM2KO and LPS challenged mice exhibited similar patterns of TBI associated inflammation. Furthermore, decreased hemispheric swelling correlated strongly with decreased ratios of Arginase1/iNOS and increased microglial expression of P2Y12.

Key words
swelling, TREM2

C3-29

EXPERIMENTAL DIFFUSE BRAIN INJURY LEADS TO CHRONIC ENDOCRINE DYSFUNCTION

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Endocrine dysfunction occurs in 35–40% of patients with a history of traumatic brain injury (TBI), which can impair health, impede rehabilitation, and lower life expectancy. The urgent clinical need necessitates investigation on the time course and underlying pathological processes. In this study we seek to model chronic endocrine dysfunction at rest and under stressed conditions. We hypothesize that diffuse TBI causes discrete neuropathology in hypothalamic-pituitary brain regions that leads to the development of endocrine dysfunction with a delayed time course evoked by stress.

In adult rats, moderate diffuse TBI (midline fluid percussion, 2.0 atm), but not sham injury, induced chronic endocrine dysfunction. Sensory sensitivity, assessed by whisker nuisance task at 28 d post-injury, was significantly increased compared to shams ($U(18) = 27.00$, $p = 0.0424$). At 54 d post-injury, prior to stress, brain-injured rats had lower plasma corticosterone compared to shams ($t(9) = 2.952$, $p = 0.0162$), as seen clinically. Restraint stress significantly increased plasma corticosterone across time in all rats ($F(3,33) = 26.80$, $p < 0.0001$). However, 60 minutes after stress onset, corticosterone was elevated significantly less in brain-injured rats compared to shams ($F(1,11) = 4.946$, $p = 0.0480$). At 56 d post-injury, depression of serum corticosterone was tested 2 h following a subcutaneous injection of synthetic glucocorticoid, dexamethasone. Dexamethasone decreased serum corticosterone equally in both groups compared to 54 d post-injury ($F(3,66) = 23.20$, $p < 0.0001$). Body weights further indicated injury-related metabolism and endocrine dysfunction. TBI significantly decreased body weight from 0-3 d post-injury ($t(17) = 3.325$, $p = 0.004$), whereas body weight from 3-56 d post-injury was significantly increased compred to sham ($t(17) = 5.066$, $p < 0.0001$), showing physiological consequences of endocrine dysfunction. Injury-related neuropathology is ongoing in relevant hypothalamic nuclei (Golgi and silver stains).

These data validate a rodent model of diffuse TBI to explore structural, functional, and hormonal mechanisms involved in the genesis and persistence of endocrine dysfunction. These and future studies will guide clinical investigations to advance diagnosis, prognosis and therapeutic approaches improving the quality of life for TBI survivors.

NIH-R01-NS065052, Phoenix-VA Healthcare System

Key words
chronic dysfunction, corticosterone, midline fluid percussion, TBI

C3-30

AXONAL INJURY IN A MOUSE MODEL OF SUBARACHNOID HEMORRHAGE

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Subarachnoid hemorrhage (SAH) from the rupture of an intracranial aneurysm shares key mechanical features with traumatic brain injury (TBI), including exposure to a sudden, global pressure wave generated by the arterial jet. It might, therefore, be anticipated that the diffuse mechanical injury of axons central to TBI pathophysiology is also an important component of injury after SAH. Elucidating these connections may lead to novel treatment approaches to both conditions. We undertook a parallel diffusion tensor imaging (DTI) and histopathology study to understand the extent of axonal injury following SAH in a mouse model. We quantitatively compared changes in white matter anisotropy indicative of axonal integrity to histological and ultrastructural evidence of axonal injury from the same tissue. DTI reveals a significant decrement in relative anisotropy in white matter regions close to the site of arterial rupture, with smaller reductions observed in more distant white matter structures. Histological analysis reveals multifocal axonal injury in a large halo surrounding the focus of bleeding. Correlation with behavioral tests suggests that axonal injury may underlie functional deficits observed after SAH. DTI analysis of human patients with SAH reveals similar decrements in anisotropy. These investigations reveal that axonal injury is a feature of brain injury following SAH, and suggest that similar pathophysiological processes may contribute to human disease. Further analysis of this phenomenon may further illuminate the processes underlying cerebral injury from SAH and TBI, provide new prognostic indicators, and suggest novel treatment modalities for this devastating condition.

Key words
subarachnoid hemorrhage

C3-31

GENE NETWORKS ANALYSIS TO ELUCIDATE THE COMPLEXITY OF TBI

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The lack of a comprehensive mechanistic understanding of the complexity of TBI pathology likely explains the poor outcomes of current therapeutics. We carried out a systems biology study to address these challenges using state-of-the art methodologies that can capture the tremendous genomic variability inherent to TBI. The unique aspect of our approach is to determine the effects of TBI on interaction of genes within a genome-wide scale to grasp the whole dimension of the pathology. We used next generation sequencing and integrative genomics analyses to determine how TBI affects gene networks that could characterize main events in the TBI pathology. We report that moderate fluid percussion injury (FPI) engages the action of master genes such as Anxa2 and Ogn to coordinate the function of hundreds of genes in the network. Increasing evidence indicates that TBI poses risks for neurological disorders such as Alzheimer's disease, and psychiatric disorders. We report that gene network reorganization in our rodent model of TBI overlaps with existing human libraries of gene-wide association studies (GWAS) for brain disorders such as Alzheimer's disease, bipolar disorder, autism, etc. These results reveal mechanistic information how TBI impacts specific gene networks which confer vulnerability to neuropsychiatric disorders. We also show that the broad spectrum of action of dietary docosahexaenoic acid (DHA) is instrumental to counteract TBI pathology by restoring gene network reorganization. These studies may set basis for development of network-based medicine, a new line of therapeutic strategy, to improve TBI outcome and prevent TBI-associated brain disorders (supported by NIH R01NS50461).

Key words
epigenetic, gene networks, genomic, GWAS

C3-32

DISRUPTION OF AUTOPHAGY AFTER TBI IS ASSOCIATED WITH LYSOSOMAL DYSFUNCTION AND NEURONAL CELL DEATH

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Disruption of autophagy, a cellular lysosome-dependent 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 brain injury induced by controlled cortical impact (CCI) in mice, we observed increased autophagosome accumulation in the cortex as indicated by the autophagic marker LC3-II in Western blot. This was confirmed by LC3 immunofluorescence and using transgenic mice expressing GFP-LC3. Like LC3-II, the autophagic substrate p62 also increased in the cortex soon after injury, peaked around day 1 and resolved by day 7. Therefore, early accumulation of autophagosome in the cortex after TBI is due to block of autophagosome degradation, rather than increase in their synthesis. This was supported by *ex vivo* experiment in which we found block of autophagic flux in brain slices from injured cortex as compared to controls. This early impairment of autophagy was at least in part caused by TBI-induced lysosomal dysfunction, as evidenced by lower protein levels and enzymatic activity of cathepsin D in the injured cortex. Accumulation of autophagosomes occurred predominantly within neurons at day 1 after injury. At that time we observed co-localization of caspase dependent (cleaved caspase 3, caspase 12) and caspase-independent (AIF) cell death markers with GFP-LC3 signal in cells around the injury site. Together, our data demonstrate that autophagic clearance is compromised at the early time points after TBI. This is at least in part due to decreased lysosomal function and likely contributes to neuronal cell loss. Autophagic flux is restored by day 7, at which point autophagy could become neuroprotective. We propose that restoration of lysosomal function early after TBI and further activation of autophagy at later time points may provide complementary therapeutic strategies to limit neuronal loss after TBI.

Key words
autophagy, autophagy flux, ex-vivo model, GFP-LC3, lysosomal function, transgenic mouse model

D1-01

METHYLENE BLUE ATTENUATES TRAUMATIC BRAIN INJURY ASSOCIATED NEUROINFLAMMATION AND ACUTE DEPRESSIVE-LIKE BEHAVIOR IN MICE

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Traumatic brain injury (TBI) is associated with cerebral edema, blood brain barrier breakdown and neuroinflammation that contribute to the degree of injury severity and functional recovery. Unfortunately, there are no effective pro-active interventions for limiting immediate or long-term neurological consequences after TBI. Therefore, the objective of this study was to determine the efficacy of methylene blue, an anti-oxidant agent, to reduce inflammation and behavioral complications associated with a diffuse brain injury. Here, we show that immediate methylene blue infusion (i.v., 30 minutes after TBI) reduced neuroinflammation, microglial activation, and improved behavioral recovery after midline fluid percussion injury in mice. Specifically, edema and inflammatory gene expression in the hippocampus after TBI were significantly reduced by MB 1 day post injury (dpi). Moreover, MB intervention attenuated TBI-induced inflammatory gene expression (IL-1β, TNF-α) in enriched microglia/macrophages 1 dpi. Cell culture experiments confirmed that MB treatment directly reversed activation of BV2 microglia by lipopolysaccharide (LPS). For example, MB intervention reduced IL-1β and increased IL-10 mRNA levels in LPS-activated BV2 microglia. Next, functional recovery was determined in mice after TBI and MB intervention. MB intervention after TBI did not prevent reductions in body weight and motor coordination 1–7 dpi. Nonetheless, MB attenuated the development of acute depressive-like behavior after TBI (7 dpi). Taken together, our data shows that immediate intervention with MB was effective in reducing neuroinflammation and improving behavioral recovery after TBI. Thus, MB intervention may reduce life-threatening complications of TBI, including edema and neuroinflammation, and protect against the development of neuropsychiatric deficits.

Key words
depression, methylene blue, neuroinflammation, TBI

D1-02

DELAYED METHYLENE BLUE IMPROVES LESION VOLUME AND BEHAVIORAL OUTCOME FOLLOWING TBI

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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 delayed MB treatment would reduce lesion volume and improve functional recovery in a rat TBI model. Anesthetized rats underwent a 6mm 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 1mm 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 T_2 on days 0, 2, 7, and 14 after TBI. Comparisons of MRI scans were made with the progression of lesion volume, behavioral analysis (cylinder test and foot fault test) (days 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 one and twenty four hour MB-treated groups lesion volume growth was smaller on day 2 compared to the vehicle-treated group by 21% and 23%, respectively ($P < 0.05$). Lesion volume in MB treated rats continued to significantly decrease in lesion volume compared to vehicle-treated rats on days 7 and 14 post-injury ($P < 0.05$). 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 days 0 and 2 ($P < 0.05$). However, MB treated rats demonstrated improved motor function by day 7 compared to vehicle treated rats, indicative of improved neurological status. In summary, 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.

Key words
methylene blue, MRI, traumatic brain injury

D1-03

HYPOTHERMIA IN TBI FOR CONTROL OF INTRACRANIAL HYPERTENSION AS THERAPEUTIC OPTION: ICP TRENDS AND GRADED HYPOTHERMIA

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Hypothermia has the potential to influence key destructive mechanism following traumatic brain injury(TBI), reduces intracranial pressure and possibly provides neuroprotection. The present study will test to titrated hypothermia for ICP reduction after TBI. The hypothesis is that therapeutic hypothermia will reduce morbidity/mortality compared to those receiving standard care alone after TBI.

This is prospective RCT to examine effects of hypothermia (32–35°C) on raised ICP after TBI. Adults with primary closed TBI with raised ICP > 20 mm Hg for ≥ 30 minutes after first line treatments and with no obvious reversible cause and with abnormal CT scan are randomized to hypothermia (32–35°C)/normothermia group. Hypothermia initiated with refrigerated 0.9% saline/maintained using surface cooling blanket. Depth of hypothermia guided by ICP with a higher pressure level warranting a cooler target temperature. Therapeutic hypothermia is maintained for at least 48 hours in treatment group but if there is inadequate response to hypothermia patients are taken up for decompressive craniectomy. Outcome in this abstract is assessed on ICP control, length of stay in ICU and hospital stay.

The result is than 28 patients (13 in hypothermia group, 15 in control group), mean age was 35.3 yrs, (and range 16–50 yrs, 27 males, mean ICP at randomization was 22.6 and 24 mm Hg in hypothermia and control group respectively. CT Marshall grade 6 was observed in 18/28 cases (traumatic SAH in 16, acute subdural hematomas in 11 cases).There were no coagulation abnormalities in either group. Mean duration of ICU and hospital stay was 10.2 days/ 9.5 days and 19.5/18.6 days in normothermia and hypothermia group respectively. Admission was longer in the control group but was not statistically significant.

The conclusion is that Hypothermia can be used safely as an adjunct to other modalities for controlling ICP in severe TBI. It is not associated with a longer duration of ICU/hospital stay or other complications when compared with controls.

Key words
hypothermia, raised intracranial pressure, traumatic brain injury

D1-04

STEM CELL TRANSPLANTATION-MEDIATED ALTERATION OF MICROGLIAL PHENOTYPES IN INJURED MOUSE BRAINS

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Neural stem cell (NSC) transplantation promotes functional recovery from brain trauma. However, the underlying mechanisms still remain largely unclear, which may hinder the exploration for a full potential of cell therapy. Given the theory that stem cell transplantation worked solely by replacing neural cells has been challenged, more studies are now focusing on the interaction between grafted and host cells. Special attention has been given to the cross-talk between grafted cells and host microglia or infiltrated macrophages. It is currently unknown whether and how grafted NSCs modulate the phenotypic changes of host microglia/macrophages following traumatic brain injury. To this end, we transplanted primed human NSCs into mouse brains 24 hours after controlled cortical impact, collected brain tissues 6 days after implantation, and then performed Immunohistochemical and western blot analyses. Human NSC transplantation not only reduced brain lesion size and decreased APP accumulation, but also favored a transition of microglia/macrophages from the inflammatory M1 type to the anti-inflammatory M2. Furthermore, most grafted cells migrated to the injury site where they mainly differentiated into neurons, and were phagocytized by either M1 or M2 cells without immune suppression. Thus, our data suggest that grafted NSCs alter the host environment by turning microglia/macrophages in the injured brain from a pro-inflammatory to an anti-inflammatory phenotype, which may enhance neuroprotection after traumatic brain injury.

Key words
anti-inflamation, grafted and host cell interaction, human neural stem cell, microglial/macrophage

D1-05

CHANGING THE OUTCOME OF TRAUMATIC BRAIN INJURY IN MICE. NO GENES. NO DRUGS

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The major goal of preclinical studies of traumatic brain injury is to discover new therapeutic interventions, but nearly all of the clinical trials based on those discoveries have failed. A new approach is to combine therapies, but it is not clear which therapies should be chosen or when they should be delivered. The goal of this study was to determine how outcomes of CCI can be altered without genetic or drug approaches, providing an experimental model of good and bad outcomes following comparable injury in the same species. In earlier studies, we showed that in aged (22–24 month old C57/BL6 mice) behavioral outcomes are worse, inflammatory responses are increased, and neuroprotective responses in the HIF-1 alpha pathway, including expression of erythropoietin (EPO), are decreased when compared with adult (4–5 months old) mice. In this study, we determined whether exercise can improve outcomes. Adult (4–5 months) mice were housed in running wheel cages (runners) for 6 weeks prior to CCI, and they ran an average of 5 km/night. Control adult mice housed in standard cages were videotaped, and they did not attempt to exercise (couch mice). Following the running period, mice were subjected to CCI, and both motor and cognitive deficits were tested. Runners showed significantly reduced deficits in the gridwalk test and improved retention scores in the radial arm water maze when compared with couch mice. Expression of EPO mRNA in the injured cortex was also increased in runners when compared with couch mice. Thus, aging worsens outcomes and exercise improves outcomes after CCI in mice, and expression of EPO is positively correlated with improved outcomes. Future studies comparing injury responses in aged mice and exercised adult mice can provide information on which mechanisms are activated at specific times following injury. Thus, these changes in injury responses that occur without either genetic manipulation or drug treatment could be used to identify specific treatment targets and appropriate therapeutic windows for combined therapies.

Key words
aging, controlled cortical impact, erythropoietin, exercise, mouse

D1-06

DEXAMETHASONE POTENTIATES RECOVERY OF THE BLOOD-BRAIN BARRIER AFTER PRIMARY BLAST INJURY *IN VITRO*

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The blood-brain barrier (BBB) has emerged as a promising therapeutic target for the treatment of blast-induced traumatic brain injury in light of recent studies reporting BBB breakdown after blast exposure. We demonstrate that post-injury treatment with dexamethasone (DEX) potentiates recovery of the BBB *in vitro*.

Mouse brain endothelial cells (bEnd.3) were cultured to represent an *in vitro* BBB model. Cells were seeded on Transwell inserts and cultured for 7 days to confluency. A shock tube with a 76 mm-diameter, 50 mm-length driver section, and 1240 mm-long driven section was used to generate blast with a 571 kPa peak overpressure, 1.06 ms duration, and 186 kPa*ms impulse. Cultures were placed in a receiver designed to mimic the skull-brain complex and mitigate wave reflections. Sham controls were processed identically to injured cultures but not exposed to blast. Injured and sham cultures were treated with DEX (10 μM) or vehicle 30 min post-injury. TEER was measured with an Endohm-12 chamber connected to an EVOMX Voltohmmeter (WPI). Hydraulic conductivity was measured using a custom device to quantify fluid flow.

Following blast exposure, DEX-treated cultures exhibited full recovery of TEER 1 day after injury compared with 3 days in untreated cultures, demonstrating potentiated barrier restoration due to treatment. BBB recovery in DEX-treated cultures was permanent up to 3 days following blast. TEER of DEX-treated injured cultures remained significantly elevated compared with untreated injured cultures and untreated shams for 3 days after blast, suggesting that treatment was associated with overall strengthening of the BBB. The time-course for potentiated TEER recovery was supported by significantly reduced hydraulic conductivity in DEX-treated cultures compared with untreated injured cultures for 3 days after blast, confirming faster recovery of barrier integrity. These results suggest utility in DEX treatment for potentiating functional recovery of the BBB to mitigate the effects of blast injury.

Key words
bEnd.3, blood-brain barrier, dexamethasone treatment, primary blast injury, recovery

D1-07

INTERACTIONS BETWEEN PIOGLITAZONE AND MITONEET AMELIORATE MITOCHONDRIAL DYSFUNCTION FOLLOWING TRAUMATIC BRAIN INJURY

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A major pursuit is currently underway for the discovery of novel neuroprotective therapeutic agents to help those suffering from traumatic brain injury, TBI. Due to the complicated nature of TBI, the most promising compounds target multiple mechanisms initiated following injury such as neuroinflammation, ROS production and mitochondrial dysfunction. Previous reports show that pioglitazone, a known PPAR agonist, can alter neuroinflammation and decrease ROS production. Additionally, pioglitazone has been found to increase mitochondrial bioenergetics, cortical sparing and functional recovery following TBI, which aligns with our theory that mitochondrial dysfunction is a pivotal link in the neuropathological sequelae of brain injury. The positive effects seen with pioglitazone seem to be independent of PPAR interaction and may be attributed to its binding affinity with a novel mitochondrial protein called mitoNEET. Therefore, we hypothesize that pioglitazone's neuroprotective mechanism is dependent on interactions with mitoNEET. To test this hypothesis we have used mitoNEET null mice and a novel mitoNEET ligand called NL-1. *Ex vivo* dose response studies show that pioglitazone can increase mitochondrial bioenergetics in isolated mitochondria with and without Ca^{2+} insult. Next, wild-type and mitoNEET null mice (pioglitazone and NL-1 study) and Sprague Dawley rats (NL-1 study) who were subjected to sham or severe controlled cortical impact (CCI) TBI surgery. Results demonstrate that pioglitazone loses its ability to increase mitochondrial respiration and provide neuroprotection in mitoNEET null mice and that treatment with a specific mitoNEET ligand (NL-1) increases cortical sparing and motor recovery following TBI. Therefore, we believe pioglitazone to be a novel mitochondrial targeting drug which is able to alter mitochondria bioenergetics following TBI through interactions with mitoNEET. Results from these studies will help to shed light on the fundamental processes involved in TBI neuropathology and may pinpoint potential novel interventions and targets for the treatment of TBI.

Key words
controlled cortical impact, mitochondria, mitoNEET, pioglitazone, traumatic brain injury

D1-08

EFFECT OF NNZ-2591 TREATMENT ON AXONAL AND SYNAPTIC PLASTICITY FOLLOWING PENETRATING BALLISTIC-LIKE INJURY IN RATS

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NNZ-2591, a novel diketopiperazine, has shown therapeutic effects in improving sensorimotor and cognitive outcome in rodent models of neurodegenerative diseases. The current study examined the potential role of NNZ-2591 in neuroplasticity following penetrating ballistic-like injury (PBBI; 10% injury severity) in rats. Adult Sprague-Dawley rats were randomly assigned into three groups: sham (craniotomy only), PBBI + vehicle (i.e. H_2O), and PBBI + NNZ-2591. NNZ-2591 (or vehicle) was administered via oral gavage at 30 mg/kg at 30 min post-injury and continued once daily thereafter for 7, 14 or 28 days. At each treatment endpoint, rats were perfused and brains were processed for histological analysis (n = 4-6/group/time-point). For detection of axonal sprouting, immunohistochemical detection of growth-associated protein-43 (GAP-43) was employed. Synaptogenesis was determined by immunohistochemistry for synaptophysin (SYN). For histological quantification, the integrated density in the hippocampal region was determined using NIH ImageJ software. In the vehicle treatment group, PBBI significantly decreased GAP-43 expression in the ipsilateral hippocampus at 7 d, 14 d and 28 d post-injury, and in the contralateral hippocampus at 7 d and 14 d post-injury ($p < 0.05$ vs. sham). Significant reductions in SYN staining were detected at 14 d and 28 d post-injury in the ipsilateral hippocampus and at 14 d post-injury in the contralateral hippocampus in the PBBI + vehicle group ($p < 0.05$ vs. sham). Continuous treatment with NNZ-2591 showed no effect on injury-induced reductions in GAP-43 or SYN expression at 7 d or 14 d post-PBBI. However, at 28 d post-injury, NNZ-2591 treatment attenuated PBBI-induced reductions in both GAP-43 and SYN expression to levels that did not differ significantly from sham controls, indicative of an intermediate treatment effect. Overall, the histological analysis indicates that PBBI induced significant reduction of axonal sprouting and synaptogenesis during sub-acute to chronic phase after injury. Furthermore, the current results show a promising trend of NNZ-2591 in promoting neuroplasticity and warrant further testing of this drug using extended treatment durations in the PBBI model.

Key words
axonal sprouting, diketopiperazine, synaptogenesis

D1-09

EVALUATION OF COMBINED ADMINISTRATION OF DEXTROMETHORPHAN AND SIMVASTATIN IN AN EXPERIMENTAL MODEL OF TRAUMATIC BRAIN INJURY

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We recently completed comprehensive Phase I monotherapy dose-response (D-R) testing of Dextromethorphan, Progesterone, Simvastatin and Cyclosporine in a rat model of penetrating ballistic-like brain injury (PBBI). Of the 4 drugs tested, Dextromethorphan (DM) showed the most consistent D-R profile across motor parameters whereas Simvastatin (SIM) showed the best D-R profile for improved cognitive outcome. In this study, isobolographic analysis (based on the concept of dose equivalence) was used to construct fixed-dose ratios of each drug to determine whether combined treatment produce additive or synergistic effects. Anesthetized rats received frontal PBBI (10% injury severity). DM and SIM were tested in pairs at the following fixed-dose ratios: 1.65/0.0019 mg/kg, 3.3/0.0038 mg/kg, 6.59/0.015 mg/kg or 13.19/0.150 mg/kg (DM/SIM, respectively). DM was administered at 30 m, 2 h, 4 h, and 6 h post-PBBI and once/day for 3 consecutive days. SIM was administered at 30 m and 6 h post-PBBI and once/day for 10 consecutive days. Motor and cognitive abilities were assessed using the rotarod and Morris water maze (MWM). In addition to being analyzed individually, the primary outcome metrics were transformed into standardized z-scores and summed to yield a

composite motor/cognitive score for isobolic analysis using the concept of dose equivalence. Results revealed a moderate trend towards improved motor performance with an intermediate treatment effect detected at the highest dose-ratio tested. In contrast, significant dose-dependent improvements were detected on the MWM task evident on measures of latency to locate the hidden platform and in percent time spent swimming around the outer perimeter of the water maze. Isobolic analysis of the composite motor/cognitive score showed clear additivity for the combination confirming that the dose of one drug can be reduced when combined with the other and in quantities that are consistent with their individual potencies.

Key words
cognitive, combination therapy, motor, PBBI, TBI

D1-10

THROMBIN DECREASES EXPRESSION OF GLAST AND INHIBITS GLUTAMATE UPTAKE IN ASTROCYTES VIA THE RHO KINASE PATHWAY

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Preclinical and clinical studies suggest that breach of the blood brain barrier (BBB) leading to extravasation of the serum proteins such as thrombin contribute to the mechanisms of post-traumatic epilepsy (PTE). The astrocyte glutamate transporters GLAST and GLT1 play a key role in regulating neuronal excitation and their levels are decreased after TBI. We examined the effects of thrombin on the expression and function of glutamate transporters in isolated rat cortical astrocytes.

Primary astrocytes were exposed to thrombin or PAR-1 activating peptide. After 24 hr recovery, GLAST and GLT1 levels were quantified by Western blotting. Glutamate uptake was measured using an enzymatic assay.

Thrombin induced a decrease in the expression of GLAST, with a corresponding decrease in the capacity of astrocytes to take up glutamate. Activation of the thrombin receptor PAR-1 with an activating peptide induced a similar decrease in the expression of GLAST and compromise of glutamate uptake. The downregulation of GLAST induced by thrombin was mediated by the mitogen activated protein kinases p38 MAPK, ERK and JNK, but inhibition of these kinases did not prevent the decrease in glutamate uptake induced by thrombin. In contrast, inhibition of the Rho kinase pathway using the specific inhibitor, Y27632, suppressed both the decrease in the expression of GLAST and the decrease in glutamate uptake induced by thrombin.

These results identify a novel mechanism for the regulation of glutamate transporters following disruption of the BBB, and implicate thrombin in the mechanisms of PTE.

Key words
glutamate, MAPK, proteases, RhoK

D1-11

REMOTE-ISCHEMIC PRECONDITIONING AS A PROPHYLACTIC METHOD TO INCREASE BIOLOGICAL RESILIENCE TO MILD TRAUMATIC BRAIN INJURY

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Mild traumatic brain injury (mTBI) accounts for the largest proportion of brain injury cases. Sports injuries and military trauma in particular have high incidences of repetitive mTBI occurrences. While the majority of cases resolve over time, a significant proportion of mTBI cases report ingoing neurological issues. Treatment to reduce the secondary cellular injury mechanisms in these vulnerable groups remains elusive. We previously developed a model of mTBI using a shock wave generating device which demonstrates hallmark features of white matter pathophysiology and persistent neurobehavioural deficits relevant to mTBI. Remote-ischemic preconditioning (rIPC) has been shown to provide protection to tissues sensitive to ischemic stress. Given the overlap in final common pathways found in ischemic injury as well as cellular mechanisms of secondary injury progression in mTBI, we hypothesized that rIPC would provide therapeutic benefit in a model of mTBI. rIPC was evaluated as a potential prophylactic treatment for mTBI incurred through primary blast exposure. Anesthetized adult male Sprague-Dawley rats were subject to 4 cycles of hind-limb ischemia applied for 5 minutes followed by 5 minutes of reperfusion. A control group consisted of rats subjected only to anesthesia. Twenty-four hours after rIPC treatment, rats were exposed to a $\sim$40 kPa primary blast. Preliminary results indicate a reduction in αII-spectrin breakdown in the corpus callosum with rIPC treatment, independent of protective effects exerted by isoflurane preconditioning. rIPC also modulated the heavy neurofilament response to primary blast trauma. Immunoblotting for HIF-1α indicated a lack of expression in all injury groups suggesting that ischemia did not play a role in the blast mTBI model. The current results suggest that rIPC may reduce pathophysiological response after mTBI, independent of ischemic signalling pathways. Furthermore, the rIPC treatment may represent a simple and non-invasive means of augmenting endogenous biological resilience to mTBI.

Key words
mild TBI, primary blast, remote ischemic preconditioning, resilience, subclinical

D1-12

ACUTE INTERLEUKIN-6 TRAJECTORIES AFTER TBI: RELATIONSHIP TO ISOLATED INJURY AND POLYTRAUMA AND ASSOCIATIONS WITH OUTCOME

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Due to the heterogeneity of injury patterns in traumatic brain injury (TBI), characterization of pathophysiology observed in isolated TBI compared with TBI + polytrauma is needed. Interleukin-6 (IL-6) is a pro-inflammatory cytokine known to be elevated after major trauma. We examined whether IL-6 temporal profiles (trajectories) differ in isolated TBI versus TBI + polytrauma and whether these profiles predict outcome. Injury type was dichotomized as 'isolated' or

'polytrauma' using Abbreviated Injury Scale (AIS) nomenclature (head/neck + other body regions). Cerebrospinal fluid (CSF) IL-6 was measured in samples collected 0-5d post-injury for 114 adults with severe TBI. Group-based trajectory analysis (TRAJ) was conducted to assess temporal IL-6 profiles. Injury type was compared to IL-6 TRAJ, which was used to predict 6 and 12 month Glasgow Outcome Scale scores. There were two distinct CSF IL-6 profiles. *Group-1* had an initial peak, followed by steady decline after d1; *Group-2* had a sustained elevation. Injury type was associated with IL-6 TRAJ group ($\chi^2 = 5.31$, $p = 0.02$). There was 70% concordance between those with TBI + polytrauma and TRAJ *Group-1*; in contrast, isolated TBI was nearly equally distributed between TRAJ subgroups. Compared to TRAJ *Group-1,* individuals in *Group-2* had an increased odds of unfavorable outcomes at 6 (OR = 3.39, 95% CI: 1.25-9.18) and 12 months (OR = 2.60, 95% CI: 1.02-6.64), after controlling for age and GCS. We conclude the presence/absence of polytrauma is associated with acute CSF IL-6 patterns. IL-6 TRAJ group classification significantly predicted 1yr outcomes. Interestingly, polytrauma complicating TBI shifted CSF IL-6 TRAJ from a sustained to a decelerating profile. Future studies should explore additional factors contributing to elevations in IL-6, and how to mitigate potentially detrimental effects on outcome.

Support: CDCR49-CCR323155; DODW81XWH-071-0701; NIH5P01NS030318.

Key words
inflammation, interleukin-6, polytrauma, traumatic brain injury

D1-13

HYPOTHERMIA AND *IN VITRO* HIGH-ENERGY TRAUMA

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Hypothermia (35°C) seems to have an impact on gene expression post-trauma in the examined human neuroblastoma cell line. Comparing 35°C with 37°C post-trauma incubation - expression appeared to be significantly different in 1428 genes.

To study hypothermia and high-energy trauma's effects on human neuroblastoma (SH-SY5Y) cells in absence of *in vivo* confounders, such as the animals' physiological thermoregulation.

In an *in vitro* model (the flyer-plate), a copper fragment becomes accelerated by means of a laser. The fragment hits a cell-culture well and causes high-energy trauma (shock-wave and cavitation) in a neuroblastoma colony. Incubation prior to trauma was at 37°C for all groups. An automatic equipment (CellIQ) incubated the colonies post-trauma at 35°C and 37°C respectively. Pictures of the colonies were taken every hour post-trauma by CellIQ. After 24 hr cells were harvested for gene array by Affymetrix procedures. Differential gene expression (up- or down-regulation) was assessed with unpaired t-test. The genes were functionally annotated using the Database for Annotation, Visualization and Integrated Discovery.

Cutoff for differential expression was at least 200% up- or down regulation, i.e. fold change (FC) ≤ -2 and FC ≥ 2, $P \leq 0.05$. 1428 genes were regulated 35°C-traumatised vs 37°C-traumatised: 518 down and 910 up between a FC-minimum at −4 and 20 folds maximum. 218 genes were regulated 35°C-traumatised vs 35°C-control: 77 down (FC-min = − 3), 141 up (FC-max = 3). 1232 genes were regulated 35°C-control vs 37°C-control: 395 down (FC-min = − 4) and 837 up (FC-max = 21).

Key words
automatic cell incubation, gene array microarray, gene expression regulation, high energy *in vitro* trauma, human neuroblastoma cells (SH-SY5Y), hypothermia, image-analysis, imaging

D1-14

MULTICENTER COMPARISON OF FIVE THERAPIES REVEALS THERAPEUTIC POTENTIAL FOR LEVETIRACETAM: OPERATION BRAIN TRAUMA THERAPY

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Operation Brain Trauma Therapy (OBTT) is a multi-center pre-clinical drug and biomarker screening consortium testing therapies for TBI. OBTT utilizes the parasagittal fluid percussion injury (FPI), controlled cortical impact (CCI), and penetrating ballistic-like brain injury (PBBI) models in rats to screen therapies at three sites using rigorous/blinded protocols. Identical groups (sham, TBI-vehicle, TBI-low dose, and TBI-high dose) are used across sites and motor, cognitive, histological, and serum biomarker outcomes assessed over 21 d. The code for each outcome is simultaneously broken across sites and therapies are given an overall score (maximum = 22 points/model). The first five therapies tested included nicotinamide (50 or 500 mg/kg IV at 15 min and 24 h), erythropoietin (EPO, 5000 or 10,000U/kg IV at 15 min), cyclosporin-A (CsA, 10 or 20 mg/kg, IV at 15 min and 24 h), simvastatin (1 or 5 mg/kg POX14 d), or levetiracetam (54 or 170 mg/kg IV at 15 min). Dosing was literature-based. The first four therapies produced modest/no effects across models. Nicotinamide showed some motor benefit and tissue sparing in CCI, EPO showed no benefit across models, CsA showed tissue sparing in FPI but toxicity in CCI and PBBI, Simvastatin showed modest motor benefit across models but no cognitive or histological benefit. Levetiracetam, however, showed benefit on multiple outcomes including on MWM and probe trial in FPI, motor function, MWM, and tissue loss in CCI, and probe trial in PBBI. In OBTT, Levetiracetam, given as a single IV bolus early post-TBI, shows promise. It merits exploration of therapeutic window, dose optimization, testing in models with second insults, and testing in our large animal model. Support: US Army, W81XWH-10-1-0623

Key words
biomarker, consortium, pre-clinical, therapy

D1-15

PROTECTIVE EFFECTS OF PHENELZINE AGAINST ALDEHYDE-INDUCED *EX VIVO* OXIDATIVE DAMAGE TO CORTICAL MITOCHONDRIA

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Following a traumatic brain injury (TBI) excessive reactive oxygen species are generated, which induce lipid peroxidation (LP) of membrane polyunsaturated fatty acids. A consequence of LP is the formation of toxic reactive aldehydes such as 4-hydroxy-2-nonenal (4-HNE) and the more reactive 2-propenal (acrolein) that can covalently bind to proteins and disrupt cellular processes. For example, the aldehydic protein adducts in mitochondria cause respiratory dysfunction and neuronal loss. We have recently shown that the drug phenelzine (PZ) possesses a hydrazine moiety enabling it to scavenge 4-HNE preventing it from disrupting mitochondrial function in the injured rat brain in parallel with a reduction in cortical contusion volume (Singh et al, JCBFM 33:593, 2013). The current study investigates the ability of PZ to protect isolated mitochondria from the more reactive acrolein. Mitochondria function was assessed by measuring the respiratory capacity of complex I and II after PZ-pretreated mitochondria were exposed to 4-HNE or acrolein. Initial dose response curves for acrolein demonstrate that all tested concentrations (1, 3, 10, and 20 μM) reduce complex I and II driven respiration in concentration-related manner. These concentrations reduced complex I driven respiration compared to untreated mitochondria by 7.8%, 11.2%, 56.6%, and 81.6%, respectively. Similarly, complex II driven respiration was reduced 32.7%, 49.4%, 64.9%, 80.8%, respectively. Pretreatment of 30 μM PZ protected mitochondria complex I & II driven respiration from 3 μM acrolein exposure ($p < 0.05$ vs. acrolein treated). In contrast, the PZ analogue pargyline (PG) that lacks a hydrazine moiety when applied in an equimolar concentration was unable to protect mitochondria from acrolein supporting the importance of the hydrazine moiety in the mitochondrial protective effect of PZ. Additionally, because PZ is able to exert a mitochondrial protective effect *in vitro* and in the injured brain (Singh et al, 2013), implies that PZ has a rate constant that can out compete acrolein's reactivity with cellular proteins.

Key words
acrolein, lipid peroxidation, mitochondria, phenelzine

D1-16

POLYNITROXYLATED PEGYLATED HEMOGLOBIN IMPROVES ACUTE PHYSIOLOGY VS. BLOOD AFTER TRAUMATIC BRAIN INJURY PLUS HEMORRHAGIC SHOCK

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Resuscitation with polynitroxylated pegylated hemoglobin (PNPH), a PEGylated bovine hemoglobin decorated with nitroxides, required significantly less fluid and produced neuroprotection *in vitro* and *in vivo* vs. lactated Ringer's (LR) in experimental traumatic brain injury (TBI) plus hemorrhagic shock (HS). Hypothesis: Resuscitation with PNPH will improve acute physiologic parameters vs. whole blood or LR after TBI + HS. Anesthetized mice underwent controlled cortical impact followed by severe HS to mean arterial pressure (MAP) of 25-27 mm Hg for 35 min. Mice ($n = 5$/group) were then resuscitated with 20 ml/kg of 4% PNPH, 20 ml/kg of autologous whole blood, or 60 ml/kg of LR. Markers of acute physiology (MAP, heart rate, blood gases, chemistries) were monitored after resuscitation for 105 minutes. PNPH-resuscitated mice had higher MAPs following resuscitation vs. blood or LR (82.2 ± 2.0 vs. 65.3 ± 3.8 and 38.4 ± 3.6 mm Hg, $P < 0.001$). Following resuscitation, both PNPH and blood-resuscitated mice had lower heart rates vs. LR (602 ± 13 and 608 ± 13 vs. 634 ± 19 BPM, $P < 0.001$). PNPH-resuscitated mice, vs. blood or LR, had higher pH (7.38 ± 0.02 vs. 7.31 ± 0.02 and 7.29 ± 0.04, $P < 0.05$) and lower serum potassium (5.4 ± 0.1 vs. 6.2 ± 0.4 and 7.8 ± 0.5 mg/dL, $P < 0.05$). Arterial oxygen saturations were higher in both PNPH and LR-resuscitated mice vs. blood (99.3 ± 0.7 and 97.1 ± 1.5 vs. $92.0 \pm 0.7\%$, $P < 0.01$). Blood-resuscitated mice, vs. PNPH and LR, had higher hemoglobin concentrations (10.9 ± 0.24 vs. 7.1 ± 0.3 and 7.7 ± 0.1 g/dL, $P < 0.001$) and hematocrit (34.4 ± 0.7 vs. 24.3 ± 1.8 and $24.1 \pm 0.5\%$, $P < 0.001$). Resuscitation with PNPH, vs. standard resuscitation (LR or blood), improved MAP and heart rate, reduced acidosis and hyperkalemia, and improved oxygen saturation, despite blood-resuscitated mice having higher hemoglobin/hematocrit. Our data support ongoing pre-clinical development of PNPH for TBI resuscitation. Support: U44NS070324

Key words
hemoglobin based oxygen carrier, hemorrhagic shock, resuscitation, traumatic brain injury

D1-17

INTRANASAL INSULIN TREATMENT OF TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) is a serious health problem that affects approximately 1.5 million people in the United States each year and causes long term cognitive deficits. After injury there is a transient but marked reduction in cerebral glucose uptake. The length and severity of this metabolic crisis is directly correlated with patient outcome. We hypothesized that administration of intranasal insulin, a treatment shown to improve cerebral glucose uptake and memory in Alzheimer's patients, will increase cerebral glucose uptake, neuronal survival and reduce glial mediated inflammation, leading to a reduction in TBI-related histological and functional impairment. To test our hypothesis, adult male Sprague Dawley rats received a moderate brain injury in the left motor cortex using the controlled cortical impact (CCI) model of brain injury. The animals were treated once a day for 7 days with either intranasal insulin (II) or intranasal vehicle (saline; IS). II treatment significantly improved the performance of injured animals on a balance beam in comparison to the IS group. Qualitative assessment of histology showed improved neuronal viability in the hippocampus of the II treated rats. In addition, markers of anti-inflammatory, pro-healing M2 microglia/macrophages were significantly increased in the II group in comparison the IS group. There was no significant increase in expression of M1 markers indicating that the drug treatment is pushing microglia toward an anti-inflammatory phenotype. In conclusion our studies indicate that intranasal insulin, a clinically proven treatment for Alzheimer's disease, increases neuronal viability, M2 activation and functional recovery following TBI.

Key words
CCI, hippocampus, insulin

D1-18

ER STRESS INHIBITOR SALUBRINAL IS NEUROPROTECTIVE AFTER TBI

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The newly translated proteins undergo post-translational modifications and folding in the endoplasmic reticulum (ER). The unfolded (misfolded) proteins are efficiently cleared by the ubiquitin-proteasome system. Injury to the cells disrupt these processes leading to increased load of unfolded proteins in ER which activates the intrinsic ER stress signaling pathways mediated by ATF6, IRE1 and PERK. All these are considered as the endogenous neuroprotective mechanisms to protect the brain under stress. However, uncontrolled activation of PERK pathway promotes cell death by inducing pro-apoptotic signaling. Using the controlled cortical impact (CCI) model of TBI in adult rats, we currently observed increased phosphorylation of PERK and its down-stream eIF2α in the ipsilateral cerebral cortex. The eIF2α phosphorylation inhibits protein synthesis and thus decreases unfolded protein load. However, we also observed induction of pro-apoptotic transcription factors ATF4 and CHOP which are down-stream to eIF2α, and further down-stream apoptotic genes PUMA and BIM following TBI. In addition, GADD34 that mediates dephosphorylation of p-eIF2α leading to translational recovery was also induced. We tested if treatment with salubrinal (a GADD34 inhibitor) following TBI prolongs the life of p-eIF2α to sustain translational arrest leading to decreased new protein load and thus neuroprotection. In adult SD rats, salubrinal treatment (1 mg/Kg at 5 min and 12 h; i.p.) increased p-eIF2α levels, curtailed ubiquitin-conjugated protein levels (both at 1 day after TBI) and decreased the cortical cavitation volume (at 7 days after TBI; by 39.3% ± 7.1%; $p < 0.05$; n = 6/group) compared to vehicle control. Salubrinal treatment (1.5 mg/Kg at 5 min, 2 h and 24 h) in adult C57/BL6 mice also significantly decreased cortical cavitation compared to vehicle control (at 7 days after TBI; by 48.7 ± 9.8%; $p < 0.05$; n = 9/group). Similar neuroprotection (42.4% ± 8%; $p < 0.05$; n = 9/group) was also seen when the first dose of salubrinal was delayed to 2 h and 4 h after CCI injury. In conclusion, these studies show that TBI leads to over-activation of PERK-mediated ER stress signaling in rodent brain and its inhibition is neuroprotective. Supported by NIH.

Key words
endoplasmic reticulum, PERK, salubrinal, therapeutic window, ubiquitination, unfolded protein response

D1-19

DOSE-RESPONSE EVALUATION OF SIMVASTATIN IN THE CONTROLLED CORTICAL IMPACT MODEL: OPERATION BRAIN TRAUMA THERAPY CONSORTIUM

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The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor simvastatin reduces serum cholesterol but also has potent inhibitory effects on neuro-inflammation and possible effects on brain edema, Akt, CBF and trophic factor production. Simvastatin was screened in the Operation Brain Trauma Therapy (OBTT) consortium for efficacy as a sustained therapy to improve neurobehavioral and neuropathological outcomes in the controlled cortical impact (CCI) model. Forty male Sprague-Dawley rats were anesthetized and surgically prepared for CCI injury (4 m/sec, 2.5-mm deformation) or sham surgery. Rats were randomized into four groups: CCI + vehicle (3% methylcellulose in distilled water), CCI + simvastatin (1mg/kg), CCI + simvstatin (5 mg/kg), and sham. Simvastatin was given PO with the first dose at 3 h after injury and subsequent doses daily for 14 d. Motor function (beam balance and walking) were evaluated on d1-5 and Morris water maze (MWM) (acquisition and probe trial) on d14-20. Rats were sacrificed on d21 to assess lesion and hemispheric volumes. In the beam balance test, the CCI + vehicle and CCI + simvastatin (1mg/kg) performed significantly worse than sham while the CCI + simvastatin (5 mg/kg) did not differ from sham. In the beam walking test and MWM acquistion, all of the CCI groups performed significantly worse than sham and neither simvastatin-treated group differed vs. vehicle. In the MWM probe trial (% time in target quadrant), there were no differences between CCI groups. Neither lesion volume nor hemispheric volume loss were reduced by treatment. Surprisingly, our study did not replicate the benefit of simvastatin shown in previous work. Similar to the fluid percussion and penetrating ballistic-like brain injury models also used in OBTT, modest benefit was limited to motor performance after CCI. Support: US Army, W81XWH-10-1-0623.

Key words
consortium, controlled cortical impact, rats, simvastatin

D1-20

MINOCYCLINE AND N-ACETYLCYSTEINE LIMIT THE HETEROGENEOUS INJURY THAT ARISES FROM A SINGLE CLOSED HEAD IMPACT

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Minocycline (MINO) and N-acetylcysteine (NAC) synergistically limit deficits in cognition and memory in a rat controlled cortical impact (CCI) model of traumatic brain injury (TBI). The combination works, in part, by the novel mechanism of repairing injured white matter by remyelination. We therefore wanted to test the efficacy of the drug combination in a closed head injury (CHI) model that produces a different brain injury than CCI. As we characterized the CHI model, we saw that a single impact to the head of adult mouse (C57Bl/6, 26-28 g) consistently produced two injury syndromes (CHI-1 and CHI-2). These two injury syndromes differ in immediate physiological responses, behavioral deficits and histological damage. Differences in recovery of normal breathing and righting reflex allowed the CHI-1 and CHI-2 groups to be separated within minutes after impact. CHI-1 mice began breathing within 30 seconds and regained righting reflex in 312 ± 42 seconds. CHI-2 mice did not reinitiate breathing and required cardiopulmonary resuscitation. Righting reflex was regained after 528 ± 72 seconds. On behavioral testing 7 days post-injury, CHI-1 mice acquired an active place avoidance task, yet had no long-term retention. CHI-2 mice were completely impaired in task acquisition. Behavioral deficits of CHI-1 and CHI-2 mice remained unchanged one month after injury. CHI-1 mice had a minor loss of hippocampal neurons and localized white matter. CHI-2 mice had widespread white matter injury and hippocampal neuronal loss. Treatment with MINO plus NAC improved cognition and memory in both CHI-1 and CHI-2

mice as well as limiting white matter injury. The CHI model was then used to titrate MINO and NAC levels. This led to an optimized MINO (10 mg/kg) plus NAC (75 mg/kg) combination that was significantly more potent in limiting behavioral deficits than the original MINO (45 mg/kg) plus NAC (150 mg/kg) formulation. MINO plus NAC is now known to limit brain injury in two TBI models, and two species.

Key words
cognition, drug combinations, heterogeneity, memory, synergy

D1-21

THERAPEUTIC POTENTIAL OF THE PROSTAGLANDIN E2 EP1 RECEPTOR IN TRAUMATIC BRAIN INJURY

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Brain injuries promote upregulation largely proinflammatory prostaglandin E_2 (PGE_2) leading to overactivation of a class of cognate G-protein coupled receptors, notably EP1 receptor involved in intracellular calcium signaling. Following ischemic and excitotoxic injuries, EP1 receptor activation exacerbates neuronal damage, whereas its activation following intracerebral hemorrhage may play a protective role. The goal of this study was to investigate translational potential of EP1 receptor as a target for new therapeutics in a preclinical model of traumatic brain injury (TBI).

The experiments were performed in wildtype (WT) and EP1 receptor knockout ($EP1^{-/-}$) mice of two age groups using controlled cortical impact (CCI). Neurological deficit scores (NDS) were assessed at 24 and 48 h, and brain pathology at 48 h after injury using immuno- and histochemistry.

CCI resulted in significant cortical lesions, hippocampal swelling and neurological deficits compared to sham (craniotomy only). The NDS after CCI were significantly higher in older mice (7-11mo) compared to young adult animals (2-4 mo) in both WT and $EP1^{-/-}$ animals. Post-treatment with a selective antagonist, SC-51089, or an agonist, 17-pt-PGE_2, had no significant effect on cortical lesions and hippocampal swelling in young adult WT mice. SC-51089 has also no effect on the NDS impaired after CCI, whereas 17-pt-PGE_2 improved NDS at 24 h in WT but not in $EP1^{-/-}$ mice. Immunohistochemistry revealed CCI-induced gliosis (GFAP) and microglial activation (Iba1) in selected ipsilateral brain regions which

This preclinical study provides, for the first time, clarification on the respective role of EP1 receptor as a potential therapeutic target for treatment of TBI. The results suggest that EP1 receptor is differentially and age-dependently involved in neuroinflammatory pathways associated with the progression of neurological and anatomical deficits, and selective EP1 ligands could be used in the clinic for treatment of certain neurological conditions following acute brain injuries.

Key words
controlled cortical impact, EP1 receptor, G-protein-coupled receptors, knockout mice

D1-22

BENEFITS OF EARLY ADMINISTRATION OF LEVETIRACETAM AFTER CONTROLLED CORTICAL IMPACT IN RATS: OPERATION BRAIN TRAUMA THERAPY

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Operation Brain Trauma Therapy (OBTT), a multi-center preclinical drug and biomarker screening consortium that evaluates TBI therapies, selected levetiracetam as its fifth medication. Despite limited preclinical TBI studies, levetiracetam emerged as a candidate given its sporadic clinical use treating posttraumatic seizures and favorable safety profile. Levetiracetam's proposed benefit in TBI (potentiation of GABAergic and calcium channel inhibition) may confer anti-convulsant, anti-excitotoxic, and other benefits. We assessed the efficacy of a single 15min post-injury IV dose (54 or 170mg/kg) on neurobehavioral/neuropathological outcomes after CCI. After randomization into 4 groups (Sham, TBI vehicle, TBI low dose, TBI high dose), 40 male Sprague-Dawley rats underwent CCI (4m/s, 2.5-mm deformation) or sham surgery followed 15min later by IV levetiracetam/vehicle administration. Motor function (beam-balance/beam-walk) was assessed on d1-5 and Morris water maze (MWM) (acquisition/probe trial) on d14-20. Rats were sacrificed on d21 to assess lesion volume/hemispheric tissue loss. After TBI, beam-balance testing improved with high but not low dose treatment ($p < 0.05$ vs vehicle). On beam-walk, all groups performed worse than sham ($p < 0.05$). Average latency to find the hidden platform on MWM increased in vehicle and high dose groups after TBI, but not low dose. Probe trial performance did not differ between groups. Levetiracetam markedly reduced hemispheric tissue loss ($p < 0.05$, high dose vs. vehicle). Early single-dose IV levetiracetam produced benefits across outcomes after CCI. Given the failure of other agents in OBTT, our data and promising findings by the consortium suggest the need for evaluation of dose optimization and therapeutic window for levetiracetam, and potential for clinical translation. Support**:** US Army, W81XWH-10-1-0623; T32-HD040686

Key words
anti-convulsant, controlled cortical impact, outcome, rat

D1-23

SPATIAL MEMORY NORMALIZATION AFTER TREATMENT WITH ANATABINE BEGINNING 9 MONTHS AFTER REPETITIVE MILD TBI

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TBI is a serious illness with long term consequences, even after mild injuries, which involve chronic neuroinflammatory and neurodegenerative pathways. Previously we reported on the potential of anatabine to affect neuroinflammation and improve memory when taken acutely after TBI. We have continued to characterize anatabine's effects in a crossover study as a continuation of our previous work.

We previously presented significant improvements in spatial memory and pathological outcome after treatment with anatabine beginning acutely after repetitive mild TBI (r-mTBI). In the previous study, we treated mice orally with anatabine, administered in their water throughout the study starting 30 minutes after r-mTBI or r-sham. Untreated mice (both r-sham and r-mTBI) received regular water. Although we did not see a significant improvement

to the neurobehavioral outcomes at acute timepoints, at a chronic timepoint 6 months after injury we saw a significant improvement of spatial memory of the anatabine treated r-mTBI mice compared to untreated r-mTBI mice, with anatabine treated r-mTBI mice performing as well as r-sham mice. At 9 months, 4 mice per group were euthanized, revealing regionally-specific reductions in IBA1 and GFAP staining in the anatabine treated r-mTBI mice.

We have continued to characterize the surviving mice using a crossover study. Both r-mTBI and r-sham mice that were previously untreated were given anatabine starting at the 9 month timepoint. Mice that previously received anatabine began receiving regular water only. The mice were re-evaluated using the Barnes maze at 12 and 18 months post-injury. Although r-mTBI mice that began taking anatabine at 9 months post-TBI initially continued to perform worse than shams at the 12 month timepoint, by 18 months there were no significant differences in spatial memory between any group. Anatabine shows potential at improving memory following TBI, mitigating against pathogenic neuroinflammation, and may have a long therapeutic window.

Key words
neuroinflammation, neuroprotection, TBI

D1-24

ACUTE OVER-THE-COUNTER PHARMACOLOGICAL INTERVENTION DOES NOT ADVERSELY AFFECT BEHAVIORAL OUTCOME FOLLOWING DIFFUSE TRAUMATIC BRAIN

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Following mild traumatic brain injury (TBI), patients may self-treat symptoms of concussion, including post-traumatic headache, taking over-the-counter (OTC) analgesics. Administering one dose of OTC analgesics immediately following experimental brain injury mimics the at-home treated population of concussed patients and may accelerate the understanding of the relationship between brain injury and OTC pharmacological intervention. In the current study, we hypothesize that acute administration of OTC analgesics following experimental diffuse TBI in the mouse will attenuate the functional consequences of TBI by modulating inflammatory responses.

Adult, male C57BL/6 mice were subjected to midline fluid percussion (mFPI) injury (1.4 atm). Experimental groups included mFPI paired with either ibuprofen (60 mg/kg, i.p.; n = 16), acetaminophen (40 mg/kg, i.p.; n = 9), or vehicle (15% ethanol (v/v) in 0.9% saline; n = 13) and sham injury paired OTC medicine or vehicle (n = 7-10 per group). At 24 hrs after injury, functional outcome was assessed using the rotarod task and a modified neurological severity score (NSS). Cortical cytokine levels were measured by multiplex ELISA at 6 hrs or 24 hrs post-injury to evaluate pharmacological effect on acute inflammation.

TBI significantly impaired motor performance as indicated by latency to stay on the rotarod ($F(3,53) = 3.688$, $p = 0.0174$). Significant neurological impairments were detected between groups as measured by modified neurological severity score ($KW(4, 57) = 27.37$, $p < 0.001$). Pharmacological intervention did not attenuate or exacerbate TBI-induced functional deficits. Six hours post-injury, brain injury increased cortical pro-inflammatory cytokines IL-6 ($F(1,30) = 4.468$, $p = 0.0430$) and TNF-α ($F(1,30) = 6.853$, $p = 0.0137$). However, levels were not affected by pharmacological intervention at 6 hrs or 24 hrs post-injury. These data indicate that acute administration of OTC analgesics did not exacerbate or attenuate brain-injury deficits which may inform clinical recommendations for the at-home treated mildly concussed patient.

NIH R21-NS072611

Key words
analgesic, behavior, inflammation, TBI

D1-25

REMOTE ISCHEMIC CONDITIONING AS PRE-HOSPITAL THERAPEUTIC INTERVENTION FOR DIFFUSE TRAUMATIC BRAIN INJURY

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Transient ischemia in the rat hindlimb – remote ischemic conditioning (RIC) – has shown neuroprotective effects following experimental stroke through indeterminate mechanisms. Traumatic brain injury (TBI) and stroke share secondary injury processes including inflammation and lipid peroxidation. This study seeks to evaluate the therapeutic potential of RIC following experimental diffuse TBI. We hypothesize that RIC will decrease neuropathology associated with diffuse TBI through modulation of inflammation and lipid peroxidation pathways.

Adult male sprague-dawley rats were trained on rotarod, beam balance, and beam walk tasks three consecutive days followed by one baseline test immediately prior to surgery. Rats were then subjected to moderate midline fluid percussion brain injury (2.0 atm) or sham injury. One hour later, rats were returned to isoflurane anesthesia and a tourniquet was applied to one hindlimb of RIC rats as proximally as possible, tightened until absence of pulse in the hindpaw, and removed after 60 minutes. Non-RIC rats received only anesthesia. Plasma was collected from all groups 6 h post-injury for analysis of cytokine levels by multiplex ELISA. Motor function was evaluated using trained tests on days 1, 3, 5, 7 post-injury. Brains were collected 7 d post-injury for histochemical analysis of TBI-associated neuropathology via silver stain and immunohistochemical markers of inflammation and lipid peroxidation.

RIC groups performed equivalently to non-RIC groups on tests of motor function including rotarod ($F(1,17) = 2.126$, $p = 0.1630$), beam balance ($F(1,20) = 0.2659$, $p = 0.6117$), and beam walk ($F(1,20) = 0.2296$, $p = 0.6370$). Thus, the RIC paradigm is a convenient, non-invasive method for inducing transient ischemia without neuromotor dysfunction. Ongoing analysis of biochemical and histological endpoints will determine efficacy of RIC to reduce neuropathological consequences of TBI. Ultimately, RIC could serve as cost-effective and feasible early intervention for TBI.

Diane and Bruce Halle Foundation

Key words
behavior, histology, ischemic conditioning, TBI, therapy

D1-26

NEUREGULIN-1 INFUSION AFTER TBI IN ADOLESCENT MICE IMPROVES COGNITIVE PERFORMANCE DURING ADULTHOOD

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Traumatic brain injury (TBI) is a leading cause of death and disability. As adolescence is a pivotal period of normal brain function development, brain trauma during adolescence often interferes with the normal acquisition of cognitive skills, with impairments that may persist into adulthood. Neuregulin-1 (NRG1) is an endogenous growth factor which an epidermal growth factor (EGF)-like core domain (eNRG1) and is involved in neuronal migration, axon pathway finding, myelination and synaptogenesis. We studied the neuroprotective potential of NRG1-β in a controlled cortical impact (CCI) model in mice equivalent to the adolescent age group. 5-week-old C57BL6 mice were subjected to CCI. At 2 h after injury, the mice were given an intravenous injection of PBS or NRG1-β, followed by a continuous infusion of PBS or NRG1-β delivered subcutaneously for 14 days with an Alzet pump. 5 months after CCI, outcomes were evaluated - including motor function, cognitive function, lesion volume, and axon integrity detected by immunohistochemistry. Age-matched un-injured mice were used as normal controls. Post-trauma treatment with NRG1-β did not result in a statistically significant change in lesion volume or motor function in comparison to the PBS-treated group. However, the NRG1-β treated mice had a statistically significant improvement in the Morris Water Maze hidden platform trials, suggesting that the NRG1-β infusion had a beneficial effect on spatial learning and memory. Improved axon staining was also seen in brain sections in NRG1-β treated mice compared to PBS-treated mice. Our data suggest that NRG1-β has neuroprotective potential in the treatment of TBI, and that its beneficial effects on the immature brain may lead to long-term benefits during adulthood.

Key words
neuregulin-1, neuroprotection, pediatric, trauma

D1-27

MULTINEUROTROPHIN EXPRESSING FETAL CELL TRANSPLANT IN PENETRATING BALLISTIC BRAIN INJURY (PBBI)

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The purpose of this pilot study was to evaluate survival of genetically modified fetal cell transplants in PBBI.

FDA approved naïve human fetal spinal cord neural stem cells were transplanted into Sprague Dawley (SD), Fischer344, or Athymic SD rats. Male rats were subjected to PBBI and two weeks later allocated to: Group1: no transplant, Group2: xenogeneic transplant. These groups were immunosuppressed via tacrolimus, mycophenylate, and depo-medrol. In Group 3, SD rat E14 cortical neural precursors lentivirally transduced to express multineurotrophin (MNTS1) were transplanted into PBBI injured SD rats. Group 3 was immunosuppressed with cyclosporine. Cells were microinjected into the peri-lesion region (400,000/rat). The brains were sectioned and assessed for cell specific markers for differentiation and immune response. The human-to-rat transplant rejection at 1 week was comparable to that in Fischer and Athymic at 4 weeks. All xenogeneic transplants were rejected by 8 weeks. In the allogeneic rat-to-rat MNTS-1 expressing transplant group, a robust graft spanning a millimeter square developed. Neurite lengths at week 1 were $\sim$150 micron, and by week 8 extended 3 millimeters from the transplant to engraft the lesion. Varicosities suggestive of synaptic densities on neurites could be seen. Most grafted cells labeled with neural markers while few labeled ambiguously with glial markers. The pilot data indicates that the inflammation response of PBBI and lack of sufficient growth factors mediate rejection of transplanted naive stem cells. However, with appropriate growth factor enhancement, allogeneic fetal transplants can survive and develop in the PBBI model. Transduction of human cells with MNTS1 should allow for their engraftment in athymic rats. These transplants can then be evaluated for safety and therapeutic efficacy.

Key words
chronic TBI, stem cell

D1-28

SEQUENTIAL BETA-BLOCKER AND CELLULAR THERAPY FOR TRAUMATIC BRAIN INJURY

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More than 6.5 million patients are burdened by the physical, cognitive and psychosocial deficits associated with traumatic brain injury (TBI) in the US, accounting for $72 billion in direct and indirect costs. Despite extensive efforts to develop neuroprotective therapies for this devastating disorder, there have been no successful outcomes in human clinical trials to date. We hypothesized that due to the complexity of TBI, there are multiple treatment windows in which different strategies may be therapeutic. Retrospective studies have shown that beta-adrenergic receptor blockers, specifically propranolol, significantly decrease mortality of TBI, but increase complications associated with inflammation. Conversely, cellular therapies have been shown to improve long-term behavior following TBI, likely by reducing inflammation. We hypothesized that a combination of acute propranolol and delayed mesenchymal stem cells (MSC) would have additive effects in treating a rodent model of severe TBI. We have found that the combined treatments are well tolerated with no adverse events, they display cumulative effects in decreasing BBB permeability at 96 hrs after injury, and they alter the number, activation, and localization of microglia 7 days after injury. Ongoing studies seek to optimize dosing and delivery, explore long-term cognitive outcome, and ultimately determine if this combinatorial therapy could be applied to increase clinical efficacy compared to the individual treatments alone.

Key words
combination therapy, mesenchymal stem cells, propranolol, TBI

D1-29

ACTIVATION OF BDNF-TRKB SIGNALING RECRUITS METABOLIC SIGNALS TO IMPROVE FUNCTIONAL RECOVERY FOLLOWING BRAIN TRAUMA

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The brain is a highly metabolic organ, such that disruptions of metabolic homeostasis can have dramatic consequences for cognitive function. TBI is followed by a state of metabolic dysfunction, compromising the capacity of neurons to sustain brain plasticity. There is a paucity of studies showing how metabolic adaptations support neuronal resilience crucial for coping with the effects of TBI. We have examined the capacity of a flavonoid derivative 7,8-dihydroxyflavone (7,8-DHF), a TrkB agonist that crosses the blood brain barrier, to improve brain metabolism and plasticity in animals subjected to fluid percussion injury (FPI). The 7,8-DHF (5 mg/kg, ip) was administered daily for 7 days until behavioral assessment. TBI resulted in metabolic disturbances, as evidenced by alterations in energy homeostasis markers (AMPK phosphorylation and SIRT1 levels) and mitochondrial biogenesis (levels of PGC-1α and TFAM). These changes were concurrent with reductions in memory function assessed with Barnes maze. Treatment with 7,8-DHF ameliorated impairments in cognitive function and energy homeostasis. 7,8-DHF also enhanced the activation of TrkB and downstream signaling such as CREB. *In vitro* studies showed that 7,8-DHF (200 and 400 nM) upregulates the levels of biogenesis activator PGC-1α, and CREB phosphorylation in N2a-neuroblastoma cells, suggesting that activation of BDNF-TrkB signaling is pivotal for synaptic plasticity and energy metabolism. The treatment with 7,8-DHF (200 nM) also elevated the mitochondrial respiratory capacity, measured by Extracellular Flux analyzer, which emphasizes the role of BDNF-TrkB signaling as mitochondrial bioenergetics stimulator. This study highlights the action of BDNF-TrkB signaling for building neuronal resilience underlying functional recovery following TBI. Results also suggest a close interplay between mitochondrial function and synaptic plasticity in the mechanisms of functional recovery after TBI (supported by NIH R01NS050465).

Key words
diet, functional recovery, metabolism, synaptic plasticity

D1-30

INTRACEREBROVENTRICULAR DELIVERY OF CHONDROITINASE ABC REDUCES POST-TRAUMATIC BRAIN EDEMA IN MICE

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Edema remains a common and often lethal complication of severe traumatic brain injury (TBI) with limited treatment options. We have previously shown that chondroitin sulfate molecules in the tissue drive edema and that chondroitinase ABC (ChABC) reduces edema by breaking down these molecules. The goal of this study was to demonstrate that intracerebroventricular delivery of ChABC reduces post-traumatic brain edema in mice.

Controlled cortical impact was used to induce post-traumatic edema on the left side of the brain in C57/BL6 mice. ChABC was delivered into the right lateral ventricle through a needle inserted through the skull under stereotactic guidance. After 24 hours, the mice were euthanized and the brains removed. A 4mm thick coronal section of the brain including the injury site was split into left and right hemispheres and weighed. The samples were dried at 95°C for three days and reweighed to determine the dry weight and water fraction.

Water fraction was significantly elevated above uninjured values on the side ipsilateral to the injury but not on the contralateral side, indicating that edema was confined primarily to the injured hemisphere. ChABC treatment reduced water fraction on the side ipsilateral to the injury from 79.1% (S.E. = 0.087%) to 78.5% (S.E. = 0.13%). The corresponding water fraction in uninjured vehicle-treated animals was 78.1% (S.E. = 0.06%).

The treatment eliminated approximately half of the edema induced by injury. This therapeutic strategy of delivering ChABC to the whole brain through the ventricular space has significant translational potential. Shunts are routinely placed in the ventricles of human patients with severe TBI to drain cerebrospinal fluid. Such shunts provide a convenient route of administration for this treatment. Future experiments will describe the biochemical mechanism of this therapy in more detail and reproduce these results in larger animals.

This work was supported by a Senior Fellowship in Biomedical Science from the Charles H. Revson Foundation.

Key words
chondroitinase, intracerebroventricular, mouse model, therapy

D1-31

CCR2 DEFICIENCY IMPAIRS MACROPHAGE INFILTRATION AND IMPROVES COGNITIVE FUNCTION AFTER TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) incites neuroinflammatory responses that include a dramatic rise in macrophages in the brain. The mechanisms of macrophage recruitment during TBI have not been defined. We determined the role of chemokine receptor, CCR2, in the macrophage response to TBI using a model of controlled cortical impact. Leukocytes were isolated from brain hemispheres of wild type and *Ccr2*$^{-/-}$ mice after TBI and evaluated by flow cytometry. *Ccr2*-deficient mice showed a 90% reduction in macrophages in the ipsilateral hemisphere compared to wild type animals one day after TBI, and an 80% reduction four days after TBI. To determine the effects the CCR2-dependent response on functional outcomes, *Ccr2*$^{-/-}$ and wild type mice were compared in behavioral tests beginning at three weeks after TBI. In open field tests, wild type animals after TBI exhibited elevated hyperactivity levels compared to sham controls. A lack of *Ccr2* partially rescued hyperactivity levels. In rotor rod testing, wild type animals after TBI showed reduced motor functions. A lack of *Ccr2* did not affect motor coordination on the rotor rod. Importantly, while TBI induced significant impairments in memory and learning in wild type mice as assessed by the Morris water maze eight weeks after TBI, *Ccr2*-deficient mice demonstrated reduced impairments in memory and learning. No difference in tissue loss was detected between genotypes after TBI. However, *Ccr2*$^{-/-}$ mice after TBI showed greater preservation of neuronal density in the hippocampus compared to wild type mice after TBI, providing a possible explanation for improved memory function. These data demonstrate that macrophage recruitment to the brain following TBI is largely dependent on *Ccr2* and that lack of *Ccr2* improves functional recovery. Therapeutic blockade of CCR2-dependent responses may improve outcomes following TBI.

Key words
behavior studies, CCR2, flow cytometry, inflammation, macrophage, traumatic brain injury

D1-32

GENETIC DELETION OF PARKIN ENHANCES RECOVERY FROM TBI

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Parkin is an E3 ubiquitin ligase that functions to target substrates for proteosomal degradation. Loss of function mutations to the gene encoding Parkin are linked to the development of autosomal recessive Parkinson's disease. Parkin is neuroprotective, protecting neurons in a variety of different stress paradigms. Little is known about Parkin function after traumatic brain injury (TBI). As TBI results in significant secondary damage, including oxidative stress, we hypothesized that Parkin would act as a neuroprotective factor after TBI. We therefore examined Parkin expression in mice after controlled cortical impact (CCI), and compared the recovery of Parkin knockout mice to control mice after CCI. We performed CCI over the somatosensory cortex of 9 week old male and female wild-type and Parkin null mice. All mice were sacrificed at 3 dpi. In wild type mice we found significantly elevated Parkin expression in the soma and axons of neurons in the peri-lesional area, but not in the lesion centre after CCI. Some microglial cells in the cortex and hippocampus also expressed Parkin after injury. Surprisingly, we found that Parkin null mice had fewer TUNEL positive cells in injured cortex at 3 dpi than wild type mice, suggesting that the absence of Parkin protected against acute cell death after CCI. The cortical lesion volume did not differ between the two groups. Parkin null male mice had significantly less GFAP immunoreactivity than wild type mice in the peri-lesional area after CCI. There was no difference in GFAP immunoreactivity in female mice. We also found increased nuclear immunoreactivity for TDP-43 in Parkin null male mice. Taken together our results suggest that the absence of Parkin enhanced some features of the recovery from brain injury. As Parkin has been linked to autophagy and mitophagy in particular, these Parkin null mice may help in the investigation of the role of these pathways in neuronal survival after TBI.

Key words
autophagy, mice, parkin, TDP-43

D1-33

CHRONIC ADMINISTRATION OF RESVERATROL AFTER MILD TBI REDUCES BETA-AMYLOID PLAQUE LOAD IN THE BRAIN OF 5XFAD MICE

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Traumatic brain injury (TBI) is a major risk factor for the development of Alzheimer's disease (AD) and the link between TBI and Alzheimer's-like dementia has been studied extensively in both animals and humans.

In this closed-head mild TBI model, the impactor tip was aligned on the skull on the sagittal suture midway between the bregma and lambda sutures. The 2-month old male 5XFAD mice were injured at a depth of 1.5 mm, velocity of 3.5 m/sec, and a delay time of 100 msec using the controlled cortical impact (CCI) device. After injury, mice were treated with a subcutaneous dose of either placebo (corn oil) or resveratrol (100 mg/kg) at 5 minutes, 12 hours (hrs), 24 hrs, 48 hrs, and 72 hrs after mild TBI. At 30 days after injury, the animals were intra-cardially perfused with 0.9% saline followed by 10% phosphate-buffered formalin. Whole brain sections were stained for beta-amyloid and GFAP (astrocytes).

In this study we found that in the placebo + TBI treatment group there was a significant increase in the number of amyloid plaques within the cerebral cortex on day 30 ($p < 0.03$) and 60 ($p < 0.05$) after injury compared to the control animals. Resveratrol treatment resulted in reduced plaque load on day 30 ($p < 0.05$) and 60 ($p < 0.05$). In the cortex an increase in the number of astrocytes was also observed on day 30 ($p < 0.04$) and 60 ($p < 0.05$) after injury, but a resveratrol-mediated decrease in the number of astrocytes occurred only on day 60 after injury.

Resveratrol treatment lowers beta-amyloid plaque load and chronic neuro-inflammation in 5XFAD mice. These results suggest that resveratrol may be beneficial in reducing chronic secondary brain injury and Alzheimer's-like pathology after suffering a mild TBI.

Key word
beta-amyloid

D1-34

MICRORNAS REGULATE MITOPHAGY AFTER TRAUMATIC BRAIN INJURY

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MicroRNAs (MiRs) are RNA molecules composed of 20–24 nucleotides that function to inhibit mRNA translation, and have key roles in normal CNS development and function, as well as in disease condition. Previously, we found that mitophagy can happen one hour after stretch in the primary cortical neurons and *in vivo* animal CCI models. In the current report, in addition, we found that mitophagy can happen in the peri-contusional human brain tissue. And furthermore, we found that one hour after mechanical stretch in primary cortical neurons and in human trauma tissue, miR-let-7i, miR-16, miR-92a, and miR-765 all significantly increased compared with sham controls; however, MiR-137, MiR-21, and MiR-10 significantly decreased. Interestingly, overexpression of MiR-137, MiR-21, and MiR-10 can suppress the mechanical stretch induced mitophagy in primary neurons, but not affect bulk autophagy. When the neurons were transfected with cadiolipin synthase (CLS), mechanical stretch only caused significant decrease of MiR-137 but not MiR-21 and MiR-10. The current data suggested that MiR-137 might regulate neuronal mitophagy through CLS-LC3 pathway. Considering the current neuroprotection strategy about mitophagy, this regulation may introduce a novel therapeutic target. Further detailed mechanism about the miRNA and mitophagy after TBI will be investigated.

Key words
microRNA, mitophagy, neuroprotection

D1-35

CX3CR1 DEFICIENCY AMELIORATES TBI-INDUCED INFLAMMATORY RESPONSE AND COGNITIVE DYSFUNCTION

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The exact role of neuron-microglia communication through CX3CL1-CX3CR1 signaling in neurodegenerative disorders remains elusive as recent studies targeting this pathway have shown both neuroprotective and neurotoxic properties. Traumatic brain injury (TBI) initiates a robust activation of microglia, which has been shown to persist for years following the initial event, and can ultimately result in neurodegeneration. In the current study we examined the effect of CX3CR1 deletion (*CX3CR1$^{GFP/GFP}$*) upon multiple pathways underlying TBI-induced neurotoxic responses both at acute (24 hrs) and chronic (3 months) time points after injury. TBI or sham surgery was induced by controlled cortical impact in *CX3CR1$^{GFP/GFP}$* mice (KO) and wild type (WT) animals. 24 hrs following TBI, KO animals had a reduced neuroinflammatory response compared to WT mice. Specifically, KO mice had significantly decreased expression of the pro-inflammatory mediators *IL-1β, TNFα, NOS2, and IL6* compared to WT-TBI mice. We next examined the effect of CX3CR1 deletion upon TBI-induced hippocampal-dependent cognitive funciton 3 months after injury using the radial arm water maze (RAWM). Although KO mice had a higher baseline for errors during day one of RAWM, they had a significantly ameliorated response (decreased errors) compared to WT-TBI mice. Isolated hippocampi from these animals were analyzed for multiple markers associated with synaptic function by Western blot analyses. Our results demonstrate that TBI alters post-synaptic NMDAr, as the NR2b- but not the NR2a subunit was significantly increased in WT-TBI mice, however this effect was abrogated in KO-TBI mice. Furthermore, TBI induced a significant increase in the Src-like kinase Fyn as well as the phosphorylation of p44/42 MAP kinase in WT mice, which again was abrogated in KO-TBI mice. Interestingly, we did observe a strong trend for increased PSD-95 in WT-TBI mice compared to sham, which was blunted in KO-TBI mice. Taken together, these data indicate that CX3CR1 deletion prevents the TBI-induced pro-inflammatory and neurotoxic response acutely, which may in part underlie the ameliorated response of TBI-induced synaptic dysfunction chronically.

Key words
behavior, CX3CR1, hippocampus, NMDAR

D2-01

HETEROGENEOUS TBI MODELS REVEAL DIVERGENT EFFECTS IN NEURONAL AND OLIGODENDROGLIAL PROGENITORS

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The regenerative capacity of the CNS must be optimized to promote repair following traumatic brain injury (TBI). Sonic hedgehog (Shh) maintains neural stem cell niches and promotes oligodendrogenesis. Accordingly, we examined whether Shh signaling contributes to neuronal (DCX+) or oligodendrocyte (NG2+) progenitor responses in two distinct models of TBI. Shh-responsive cells were heritably labeled in vivo using *Gli1CreERT2* transgenic mice crossed to R26-YFP or R26-IAP reporter lines. Reporter expression was induced by tamoxifen administration on 2-3 d post-TBI. Controlled cortical impact (CCI) onto the dura produced injury to the cerebral cortex. Following CCI: a) reporter labeled cells decreased in the ipsilateral cortex, b) DCX+ cells were not found in the lesion penumbra, and c) YFP+ and DCX+ YFP+ cells increased in the subventricular zone (SVZ). In the alternative TBI model, impact onto the skull produced traumatic axonal injury (TAI) in the corpus callosum. Following TAI: a) YFP+ cells within the SVZ decreased at 2wks and recovered by 6wks, b) NG2+ cells were increased in the cerebral cortex, and showed a similar trend in the corpus callosum, and c) In all regions, NG2+ cells were rarely labeled with YFP. Overall, YFP+ cells were extremely rare in the corpus callosum of non-injured mice and after either TAI or CCI, or even after microinjection of a Smo agonist (SAG) into the corpus callosum. After SAG microinjection, YFP+ cells and NG2+ cells increased in the SVZ but were not double-labeled, indicating an effect of Smo signaling without Gli1 transcriptional activation in NG2 cells. Our findings show roles for Shh signaling in both neuronal and oligodendroglial progenitor responses, with differential downstream effectors of the pathway. Importantly, cortical versus white matter damage from TBI resulted in opposite responses of Shh-activated neural stem cells within the SVZ. Supported by the NMSS and the DoD in the Center for Neuroscience and Regenerative Medicine (CNRM).

Key words
neural stem cell, oligodendrocyte progenitor, sonic hedgehog, subventricular zone

D2-02

CHARACTERIZATION OF BLAST-INDUCED VESTIBULAR INJURY IN RATS

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Blast exposure is the most common cause of traumatic brain injury (TBI) in warfighters. Nearly 60% of blast TBI victims exhibit hearing loss, tinnitus, dizziness and balance disorders. To date, the etiologies of these injuries are largely undefined. A high fidelity animal model is critical to define the mechanism(s) of injury and develop therapeutic strategies for blast-induced neurobehavioral deficits. In this study, we used an air-driven shock tube to simulate primary blast and investigated the pathological effects of blast exposures on central and peripheral auditory/vestibular systems. Anesthetized rats (Sprague Dawley, male, 350 g) were tautly secured in a transverse prone position 2.5 ft within the mouth of a 1 ft diameter shock tube with the right side facing the oncoming shockwave. Rats were exposed to two closely coupled shockwaves (peak total pressures of 5, 12 or 19 psi) separated by 30 sec. Rats were euthanized at varied intervals (6 h, 24 h, 7 d and 14 d) post injury and tissues underwent histological and RNA analyses. All rats received rotarod training prior to and testing after blast exposures for evaluation of motor coordination and balance. Compared to a single blast insult, repeated blast exposures significantly impaired motor coordination. Intensity-dependent blast-induced damage to middle and inner ears was evident with no significant differences between left and right ears. Labyrinthine hemorrhage was prominent at 24 h up to 14 days after blast exposure. Repeated blast exposures caused significant axonal degeneration and glial cell proliferation in the central vestibular signal processing regions of the brain, and also triggered multiple gene expression changes that are associated with DNA repair, neural growth, inflammation and pain. These findings indicate that both peripheral and central vestibular systems are vulnerable to blast injuries, and are particularly disrupted by closely coupled repeated blasts. Neuroinflammation, which occurred during the early phase post injury, could be a major factor leading to secondary neuronal damage.

Key words
blast TBI, inflammation, motor coordination, pathology, vestibular system

D2-03

PRIMARY BLAST DOES NOT INCREASE VULNERABILITY OF BRAIN TO SUBSEQUENT PRIMARY BLAST OR GLUTAMATE EXPOSURE

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Soldiers who use explosives to breach perimeters can experience 20 explosive detonations during 5 days of practical training and report symptoms of traumatic brain injury. Non-blast injury increases vulnerability of the brain to subsequent mechanical or excitotoxic injury. It is unclear if primary blast increases the brain's vulnerability to subsequent injury, worsening outcome for soldiers exposed to blast.

Organotypic hippocampal slice cultures (OHSC) were generated from P8-10 rat pups. A shock wave was generated with a shock tube (424 ± 6.4 kPa, 2.3 ± 0.3 ms, 248 ± 3.4 kPa-ms). OHSC were placed in a fluid-filled receiver at the exit of the tube. Sham cultures were treated identically except the shock tube was not fired. For repetitive blast studies, OHSC received 3 blast exposures within 10 minutes. For blast and glutamate studies, OHSC received blast alone, blast followed by glutamate (2.5 mM, 3 hours), or sham followed by glutamate. Cell death was quantified as the percentage area of a specific region of interest (ROI: DG, CA3, or CA1) exhibiting propidium iodide fluorescence above a threshold. As a positive control for cell death, OHSC were treated with glutamate (10 mM, 3 hours) following experimentation.

Cell death did not increase significantly following repetitive primary blast (blast: ROI < 1%, n = 18; sham: ROI < 1%, n = 10). There was no significant difference among samples receiving blast and glutamate (ROI < 1.5%, n = 6), blast alone (ROI < 1.5%, n = 6), or glutamate alone (ROI < 2%, n = 6). Cell death induced by 10 mM glutamate (63% < ROI < 90%, n = 18) indicated OHSC contained viable cells that were not killed by the other injury paradigms.

These data suggest that primary blast does not increase brain tissue vulnerability to subsequent glutamate or primary blast exposure. Our data suggest that poor outcome after repetitive blast exposure may be attributed to other blast-loading mechanisms such as tertiary blast injury (i.e. inertia-driven injury), which have known potential to injure brain.

Key words
blast, cell death, glutamate, hippocampus, shock tube, slice culture

D2-04

CELLULAR MECHANISMS OF PRIMARY BLAST- INDUCED TRAUMATIC BRAIN INJURY: SHOCK-WAVE NEUROTRAUMA

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Blast-induced traumatic brain injury (bTBI) is one of the most prevalent injuries of American soldiers. Blast related TBI are conventionally divided into four distinct phases: primary, secondary, tertiary, and quaternary. Primary blast injuries occur as a direct result of blast-wave induced changes in atmospheric pressure (barotrauma). While primary blast forces are reported to contribute to brain injury, the exact mechanism(s) by which primary blast damages the brain is poorly understood. Blast-related pathologies are likely the results of blast loading conditions such as pressure duration, peak magnitude, and rate of pressure change. The focus of this study was to gain a better understanding of the primary blast injury mechanism by observing the molecular response of primary brain cells exposed to a shock wave. We utilized a novel shock wave generator (SWG) that uses exploding wire in water to create the surge of pressure. Primary mixed neuronal - glial cell cultures were blasted in the SWG at pressures ranging from 5–15 psi for duration of less than one millisecond. RNA was extracted at several time points post exposure and Real-time PCR (RT-PCR) was performed to observe the gene expression of cytoskeletal, astrocyte, and mechanotransduction markers. Results indicate cells exposed to shock wave overpressure have cytoskeleton and membrane disruption which lead to an increase of cell apoptotic markers (Bax/Bcl2) and a decrease in cellular proliferation markers (MAP2k1) over time. At 24 hours post blast exposures, cells had significantly higher gene expression levels of Piezo2 ($p < 0.003$) as compared to the control. Within 24 hours after exposure, the cells also showed an increase in relative GFAP gene expression as compared to the sham. This study indicates that shock wave overpressure leads to membrane damage which could have led to cell death and a decrease in proliferation.

Key words
blast, traumatic brain injury

D2-05

EFFECTS OF MILD BLAST-INDUCED NEUROTRAUMA ON BLOOD-BRAIN BARRIER PERMEABILITY

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The blood-brain barrier (BBB) regulates permeability of molecules between the CNS and vascular circulation. Although much is known of BBB integrity in other TBI models, effects of mild blast-induced neurotrauma (BINT) on BBB remain unknown.

Adult, male rats were exposed to BINT using a device driven by blank nail gun cartridges. Cerebral blood flow (CBF) and mean arterial blood pressure (MAP) were recorded for one hour post-sham or BINT injury by laser Doppler flowmetry (LDF) and tail artery, respectively. Cerebral vascular reactivity was determined in isolated middle cerebral arterial segments (MCA) following sham injury or BINT. The integrity of the BBB at acute time points following sham injury or BINT was determined by Evan's Blue (EB) extravasation quantified via fluorescent signal detection using an *in vivo* imaging system (IVIS). Examining the role of peroxynitrite (ONOO-) in blast-induced BBB permeability changes, ONOO- scavenger, penicillamine, was injected following sham injury or BINT. Sham and BINT animals also performed Morris water maze (MWM).

Following BINT, MAP significantly decreased to 39.81% of baseline values ($P < 0.0001$; Sham, n = 6. BINT, n = 12). Cerebral perfusion was significantly reduced to 43.05% of baseline ($P = 0.0054$; Sham n = 6, BINT n = 12) following BINT. Dilator responses to reduced intravascular pressure in MCA were reduced significantly by BINT ($P < 0.0001$; Sham n = 4, BINT n = 12). EB extravasation was significantly greater 30 mins, 120 mins, 24 hours, and 3 days post-BINT ($P < 0.0001$; per time point Sham n = 5, BINT n = 5). Significantly less extravasation occurred in penicillamine-treated versus untreated BINT animals at 30 mins ($P < 0.0001$). MWM latencies were significantly longer ($P < 0.01$) at 24 hrs in BINT animals.

CBF reductions with normal MAP suggest BINT significantly increased cerebral vascular resistance. Additionally, impaired vasodilation in MCA segments suggests autoregulation impairment by BINT. These observations suggest BINT is associated with significant cerebral vascular injury. BINT-induced increases in EB extravasation indicate an acute breakdown of BBB that was reversed by $ONOO^-$ scavenging, suggesting a role of ONOO- in BINT-induced BBB dysfunction.

Key words
behavior, blast injury, blood-brain barrier permeability, peroxynitrite

D2-06

A NEW RODENT MODEL OF PEDIATRIC SPORTS-RELATED CONCUSSION

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CDC data indicates that over 50% of all traumatic brain injury (TBI) occurs in individuals less than 24 years old. The majority of these injuries are mild and, increasingly, they are sports-related. In order to model a sports-related injury we attached a metal disc directly to the skull and then impacted this disc using the controlled cortical impact device. The metal disc acts as a helmet to diffuse the force across the skull allowing for concussive injury in the absence of skull fracture. To test this model in the p35 rat, we generated a range of injuries by using a fixed depth of penetration (5 mm) and varying the piston velocity from 2 to 5 m/s. To assess outcome, we compared performance on the rotarod, ladderwalk, and Morris water maze between injured rats and sham controls in the first 10 days following injury. Regardless of piston velocity, animals experienced minimal periods of unconsciousness, and were ambulatory within 15 minutes. Animals with a 2 m/s injury (mild) had neither a motor nor spatial learning deficit. Animals with a 5 m/s injury (moderate) also displayed no motor deficit; however, latency to find the hidden platform in the water maze was significantly increased ($p < 0.05$) as compared to sham animals. Based on these initial data we included two additional groups with repeat injury: mild + mild or mild + moderate with a 1 hour inter-injury interval. Similar to the single injuries, no significant motor deficits were observed. Surprisingly, both groups performed similar to sham animals in the water maze. It is clear from both clinical experience and these current data that impacts onto a helmet can create a concussive injury leading to cognitive deficits. Our data also highlights the complexity and diversity of outcome observed following repeat concussive injury. Therefore, further development of animal models is critical to our understanding of how to care for young patients who have experienced concussions due to a sports-related injury.

Key words
repeat concussion, sports-related injury

D2-07

ELUCIDATING THE KINEMATICS AND PATHOBIOLOGY OF BLAST-RELATED TRAUMATIC BRAIN INJURY AND SEQUELAE IN A MOUSE MODEL

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Traumatic brain injury (TBI) resulting from blast exposure is a leading cause of death and disability associated with the recent military conflicts in Iraq and Afghanistan. We and others have reported evidence that links sports-related TBI with later development of chronic traumatic encephalopathy (CTE), a tau protein-linked neurodegenerative disease (Omalu, 2005, 2006, 2010; McKee, 2009, 2010, 2013). We previously reported the first case series of postmortem brains from blast-exposed military veterans and found evidence of CTE neuropathology that was indistinguishable from the neuropathology observed in brains from the youngest athletes with verified CTE studied to date (Goldstein, 2012). In the same study, we showed that C57BL/6 mice exposed to a single blast developed CTE-linked neuropathology, axonopathy, microvasculopathy, and neurodegeneration (Goldstein, 2012). Blast-exposed mice demonstrated persistent cognitive deficits that correlated with impaired axonal conduction and defective synaptic neurotransmission in the hippocampus. Collectively, these abnormalities recapitulate core clinical features of TBI and CTE in humans (Stern, 2013). Here we used metallomic imaging mass spectrometry, flow cytometry, cortical slice electrophysiology, and neurobehavioral testing to show that single blast exposure induces blood-brain barrier dysfunction, peripheral monocyte infiltration, chronic neuroinflammation, and defective cortical neurotransmission in blast-exposed mice. Two-axis high-speed videography (10 μsec capture rate; 100 kHz) conducted during blast exposure or a kinematically-equivalent mechanical analogue confirm the pathogenic contribution of traumatic head acceleration to acute and chronic effects of blast neurotrauma. These results provide additional mechanistic evidence linking blast exposure to acute TBI and chronic sequelae, including CTE.

Key words
blast, CTE, murine model, neuropathology

D2-08

BLAST-INDUCED TBI IN MICE ELICITS A BIPHASIC DECREMENT IN THE PERG THAT CORRELATES WITH RETINAL GANGLION CELL ACTIVITY

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Our goal was to determine whether retinal ganglion cells (RGCs) are damaged by blast-mediated traumatic brain injury (TBI)

After blast-mediated TBI, analysis of RGC structure and function was performed using optical coherence tomography (OCT) and pattern electroretinogram (PERG) 7 days, 5 weeks and 4 months later. Individual RGC physiology was monitored using a multielectrode array (MEA). Spontaneous and light-evoked responses for each RGC were measured at each time point. Dendritic arborization of individual RGCs was analyzed using GFP-labelled RGCs.

PERG amplitude decreased 7 d after blast injury, which recovered to baseline 5 weeks post injury. PERG was significantly decreased 4 months post injury. Decreased thickness of the RGC complex layer was observed by OCT at each time point.

Seven days post injury, spontaneous RGC activity was slightly increased, while the median amplitude of responses to light OFF-set increased significantly with decreased response duration.

Five weeks post injury, spontaneous activity, the median ON response amplitude and response duration, and the OFF response amplitude were all significantly increased.

Four months post injury all measures of RGC physiology had recovered to near-normal values. Cell counts of the entire retina and dendritic analysis revealed significantly decreased RGC number and abnormal dendritic fields, which correlated with abnormal RGC receptive fields observed with MEA.

TBI induces dramatic alterations in RGC physiology after an initial period of relatively normal function. The return to normal RGC function at later time points may reflect surviving RGC subpopulations that accommodated for a substantial loss of RGCs after injury. A better understanding of RGC physiology after blast exposure will help in the development of improved clinical testing and treatment of those suffering from TBI.

Key words
retinal ganglion cell, vision

D2-09

OVERPRESSURE BLAST INJURY INDUCED STRUCTURAL AND FUNCTIONAL CHANGES IN THE BRAIN AND BASILAR ARTERY

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Overpressure blast-induced brain injury (OBI) is a common problem for military population. It leads to progressive pathophysiological changes in brain. Therefore, we investigated the structure and function of the basilar artery (BA) following OBI.

Male Sprague Dawley rats (250–300 g) were divided into Control (Naive), single OBI [30 psi peak pressure, 1-2 ms duration], and repeated (every three days) OBI (r-OBI). Cortex and cerebellum tissues were taken 24 h post injury. BA was cannulised in the pressurized system and vascular responses to KCl, acetylcholine (ACh) and diethylamine (DEA)-NONO-ate evaluated.

Neurological status was impaired in OBI and r-OBI groups (4.16 ± 1.5, 3.71 ± 1.4 respectively vs 0.66 ± 0.5 in control). A significant increase ($p < 0.05$-0.001) was detected in malondialdehide – an index for lipid peroxidation-levels in OBI and r-OBI groups in cortex and cerebellum. A significant decrease was detected in glutathione (GSH) levels in r-OBI compared with control group in cortex ($p < 0.01$) and cerebellum ($p < 0.05$). Myeloperoxidase activity – an index for neutrophil infiltration – was significantly ($p < 0.01$-0.05) elevated in r-OBI. Additionally, tissue thromboplastic activity, a marker for coagulation, was significantly increased in both regions, indicating a tendency for bleeding. Edema and protein levels of NGF and NFKB were significantly ($p < 0.01$) increased in cortex after r-OBI. Furthermore, the GFAP and Iba1 immunoreactivity also demonstrated cortical injury. Endothelin contractility was increased and ACh relaxation was decreased in BA. However, impaired DEA-induced dilation and increased wall thickness to lumen ratio were observed only in the r-OBI.

Single OBI causes endothelium-dependent and -independent alterations in BA function and structural changes in the artery wall. It may be a result of the increased oxidative stress and concomitant decrease in antioxidant levels.

Key words
basilar artery, blast injury, brain, vascular

D2-10

ABSTRACT TITLE AXONAL INJURY AND MICROGLIAL ACTIVATION IN MICROPIGS FOLLOWING DIFFUSE BRAIN INJURY: AN OBTT CONSORTIUM REPORT

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Traumatic brain injury (TBI) remains a major heath care concern. Although our knowledge of the complex pathologies associated with TBI has progressed and many therapeutics have shown promising results in rodent models of TBI, this efficacy has been limited when translated to humans. Due to this low success in human translation, there has recently been a call for the development of higher order animal experimental models to better evaluate potential therapeutics prior to clinical study. With this goal in mind we have begun characterization of a central fluid percussion injury (CFPI) model of mild diffuse TBI in the adult micro pig. Assessment of diffuse axonal injury (DAI) was achieved by computer assisted counting of axonal profiles exhibiting accumulation of both the C and N-terminus fragments of amyloid precursor protein (APP). The proportion of morphologically altered activated Iba-1 + microglia was also quantitatively analyzed using stereological principals. In this model, macroscopic examination of the brain at six hours post-TBI revealed no contusion or hematoma formation and only minimal subarachnoid hemorrhage, consistent with mild diffuse TBI. Analysis of multiple brain sites revealed DAI, which was particularly abundant in the thalamus and corpus callosum, with the numbers of damaged axons averaging 11.9 swellings/0.72 mm^2 in the thalamus and 80 swellings/0.72 mm^2 in the corpus callosum. Activated microglia were primarily identified in areas associated with DAI, with the suggestion that these cellular responses are linked. The consistent spatial and temporal features of DAI in this animal model are reminiscent of those seen in humans, suggesting that this constitutes an excellent animal model for future drug and biomarker screening. This work was performed as a component of the Operation Brain Trauma Therapy consortium, which is supported by the US Army grant W81XWH-10-1-0623.

Key words
immunocytochemistry, microglia, micropig, ultrastructure

D2-11

CHARACTERIZATION OF A BLAST-INDUCED BRAIN AND EYE INJURY MODEL IN RATS

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Non-penetrating eye (retina) and brain injuries, often caused by blast overpressure (BOP) shock waves, have emerged as a significant threat to warfighters in current theaters of operation. Previous research using rodent models of BOP demonstrated reproducible injury to the eye and brain, as assessed by electroretinography (ERG) and histopathology. We further characterized this BOP injury model by examining the effect of various head orientations in relation to the oncoming BOP wave on the extent of eye injury in the rat.

Adult male rats were secured in a compressed air driven shock tube with either the right eye (side-on) or the snout (face-on) facing toward the oncoming shock wave and then exposed to a single 20 psi BOP wave. The animals were then assessed at 1, 7 and 14 days post-blast along with non-blasted sham animals utilizing ERG measurements and histopathological assessments.

At 2 weeks post-blast, side-on blasted rats versus sham animals showed significantly decreased ERG waveform amplitudes (approximately 30% from shams) and severe neuronal degradation within the retina and brain visual processing centers which could indicate functional visual deficits in the blasted animals. However, the face-on blasted rats showed minimal ERG waveform decrement or histopathologic evidence of injury, quite similar to sham animals.

We have demonstrated a reproducible method of studying BOP-induced eye and brain injuries in rats. Differences in eye and brain injury between the side-on and face-on orientation might be due to deflection of the shock wave away from the eyes in the face-on animals, owing, in part, to the conical morphology of the rodent skull. We conclude that the side-on orientation offers a reproducible model of BOP-induced eye and visual processing center brain injury in the rat and that it is suitable for further preventive and treatment paradigms.

Key words
blast injury, eye injury, TBI, vision processing centers

D2-12

A NEW MODEL OF TRAUMATIC BRAIN INJURY (TBI) SIMULATING PENETRATING INJURIES USING A CAPTIVE BOLT IN SWINE

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TBI induced by explosives/blast is the predominant head injury mechanism in current military conflicts. However, no model accurately mimics direct brain impact injuries by shrapnel or flying objects. In lateral fluid percussion, fluid wave transmission to the intact dura does not provide the complexity of injury seen in blast. While blast injuries performed in a tube replicate the ideal blast wave found in open-air explosions, they omit injuries due to shrapnel or flying objects. Open-field explosions have a less controllable environment, making it more difficult to standardize. We propose the use of a captive bolt to simulate brain injury secondary to direct skull impact of flying objects and resulting penetrating brain injury.

We built a customized plexiglas structure that held a concussion stunning captive bolt gun in place and provided adjustments for angle and depth of bolt impact. Sixteen anesthetized swine (30 kg) had scalp removed on the frontal part of the head. The tip of the gun was placed perpendicular to the exposed skull at a distance of 2.5cm. Yellow single cartridges (175m/s) were used to inflict a single hit on the frontoparietal lobe. Animals were invasively monitored for 6 hours. After euthanasia, a full necropsy was performed.

Bolt impact produced multiple skull fractures with non-lethal brain penetration, resulting in acute hypotension, apnea, bradycardia and intracranical hypertension. Gross necropsy showed consistent injury patterns. Hemorrhage volumes, fibrin deposits and neuronal loss were quantifiable in histopathology and were significantly higher than in fluid percussion control animals.

In this model, we showed a reproducible method of simulating penetrating traumatic brain injury in swine. This model may be helpful in studying open, penetrating, traumatic injuries similar to the ones encountered in combat or civilian head trauma casualties.

Key words
captive bolt, penetrating head injury model, swine

D2-13

COMBINED HYPOXEMIA & HEMORRHAGIC SHOCK WORSEN MOTOR BUT NOT COGNITIVE FUNCTION AFTER PENETRATING BALLISTIC-LIKE BRAIN INJURY

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The purpose of this study was to determine the extent to which additional insults, such as hypoxemia (HX) and hemorrhagic shock (HS), may worsen neurofunctional deficits following unilateral frontal penetrating ballistic-like brain injury (PBBI) in rats. Adult Sprague-Dawley rats were randomly assigned into 6 groups: (1) Sham (2) 5% PBBI (3) 10% PBBI (4) HX + HS, (5) 5%PBBI + HX + HS, (6) 10%PBBI + HX + HS. In the combined injury groups, HX ($P_aO_2 = 30$-40 mm Hg) was initiated 5 minutes following PBBI or sham procedures and maintained for 30 minutes. After restoring normoxia, HS (MAP = 40 mmHg) was initiated and maintained for 30 minutes. Motor function was assessed using the rotarod task at 7 and 14 days post-injury (DPI) and cognitive function was assessed in the Morris water maze (MWM) task from 13-17 DPI. PBBI produced significant decrements in motor performance (vs. sham and HX + HS groups) that were more prominent following 10% PBBI vs. 5% PBBI. Additional insults (HX + HS) significantly worsened motor functions following 5% PBBI but not 10% PBBI. Both 5% and 10% PBBI produced significant spatial learning and memory deficits in the MWM task (vs. sham control and HX + HS groups) with increased deficits evident following 10% PBBI vs. 5% PBBI. However, while rats subjected to the 5% PBBI + HX + HS injury combination showed a trend toward worsened cognitive performance (vs. 5% PBBI), this was not statistically significant. No difference in cognitive performance was detected between 10% PBBI and 10% PBBI + HX + HS groups. Overall these results suggest that 10% unilateral frontal PBBI produces motor and cognitive deficits which may exceed a sensitivity threshold capacity. In contrast, 5% PBBI produces a lower, albeit significant, magnitude of deficits and thus provides a more sensitive screen for evaluating the cumulative effects of additional insults. Additionally, the current results suggest that the cumulative effects of additional insults such as HX + HS may have more overt effects on motor vs. cognitive abilities in the PBBI model.

Key words
cognitive, hemorrhagic shock, hypoxemia, motor, neurobehavior, penetrating ballistic-like brain injury

D2-14

PENETRATING BALLISTIC-LIKE BRAIN INJURY PROMOTES TIME-DEPENDENT CELL PROLIFERATION IN ADULT RAT HIPPOCAMPUS

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Research has shown that the adult hippocampus retains the ability to produce neural precursor cells and replace lost cells in response to brain injuries. The current study examined the time course of penetrating ballistic-like brain injury (PBBI)-induced cell proliferation in adult rat hippocampus. Unilateral frontal PBBI (10% injury severity) or craniotomy (sham control) was performed on isoflurane anesthetized Sprague-Dawley rats. To evaluate cell proliferation at specific post-injury time points, BrdU (50 mg/kg x 3 i.p. injections delivered at 4 h-intervals) was initiated at 24 h prior to each experimental endpoint. At 24 h, 48 h, 72 h and 7 days post-injury rats were perfused and brains were processed for fluorescence immunostaining for BrdU, GFAP and Iba1. Minimal levels of BrdU-positive cells were detected in the brains of sham controls, and at 24 h and 7 days post-PBBI. However, a dramatic increase of BrdU-labeled cells was detected at 48 h and 72 h post-PBBI in ipsilateral and contralateral hippocampal dentate gyri (DG). Further analysis was conducted to evaluate the spatial distribution of BrdU-positive cells in hippocampal DG at 48 h and 72 h post-PBBI. The results indicate that the majority of the BrdU-positive cells were located throughout molecular layer and hilus in the DG, accompanied by a few BrdU-positive cells scattered in the subgranular zone where neural stem cells reside. Molecular layer and hilus in the DG are regions where gliogenesis mainly occurs and therefore, the majority of the BrdU-labeled cells observed in the current study are potentially gliogenic. To confirm this, additional cellular markers for astrocyte (i.e. GFAP) and microglia (i.e. Iba1) were used to confirm the phenotype of these newly generated cells following PBBI. BrdU-positive cells were primarily co-labeled with Iba1, and to a lesser extent, with GFAP, suggesting that they are proliferating microglia and astrocytes. Overall, the robust upregulation of glial proliferation during acute phases after PBBI may reflect an increasingly unfavorable environment for newborn neurons, potentially leading to further cell loss.

Key words
cell proliferation, gliogenesis, hippocampus

D2-15

COMPREHENSIVE EVALUATION OF CHRONIC SPATIAL LEARNING AND WORKING MEMORY DEFICITS FOLLOWING CLOSED-HEAD CONCUSSIVE INJURY IN RATS

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This study was designed to identify optimal Morris water maze (MWM) paradigms for evaluating cognitive abnormalities following closed-head concussion leading to mild traumatic brain injury (mTBI). For this purpose, all rats were exposed to a series of MWM tasks designed to assess: (1) spatial reference memory using a spatial learning task to find the hidden platform (two trials/day for 4 consecutive days), (2) memory retention using a missing platform (probe) trial, (3) working memory using a delayed matching-to-place task (2 pairs of trials). Adult Sprague-Dawley rats received either anesthesia (sham) or repeated projectile concussive impact (rPCI; 4 consecutive PCIs at 1 hr interval). At 1 month post-injury, results of the spatial learning task showed that the average latencies to locate the hidden ''escape'' platform were significantly longer in rPCI rats over the last two days of the MWM testing compared to sham controls ($p < 0.05$). In the memory retention task, rPCI rats also spent significantly less time in the platform zone searching for the missing platform during the probe trial ($p < 0.05$). On the working memory task, rPCI-injured animals showed a trend toward worse performance, but this failed to reach statistical significance compared to sham controls ($p = 0.07$). At 6 months post-injury, no differences were detected between rPCI and sham controls on either the spatial learning or probe trials. However, rPCI rats exhibited significantly worsened working memory performance compared to sham controls ($p < 0.05$). Overall, the results indicate that the MWM is capable of detecting cognitive deficits following mTBI and thus may be useful in assessing the effects of single vs. repeated injuries induced at varied intervals in the PCI model. Furthermore, the results show that rPCI produced significant cognitive deficits in both spatial learning abilities and in working memory abilities in a time-dependent fashion that may be indicative of progressive pathology and warrant further investigation. Funded by CDMRP/DHP Grant W81XWH-12-2-0134.

Key words
chronic effects, concussion, spatial learning, working memory

D2-16

CAUSES OF INJURY VARIATION IN A PORCINE THORACIC CONTUSION MODEL

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Reproducible spinal cord injury (SCI) contusions are necessary for assessment of safety and efficacy of experimental therapies. We conducted a series of 93 T8 contusions in Yucatan minipigs to test cellular, neuroprotective, and rehabilitative therapies; evaluating locomotor outcome using an ordinal 10-point scale (Miami Porcine Walking Scale-MPWS). Despite high mechanical reproducibility of the Miami Porcine Impactor, we find variations in injury magnitude. Severe injuries causing initial complete paraplegia lead to approximately 50% of pigs recovering weight-bearing and stepping, while the other 50% do not (4–8 months post-contusion).

A multivariate model was constructed to determine the correlates that may predict variations in tissue preservation and locomotor outcome. Independent observers were trained such that inter-observer MPWS score variation was $< 0.5/10$ points. Input variables to the model include impact force in Newtons, the magnitude of post-injury changes in heart rate and blood pressure, the size of injury signal measured using ultrasound, and the presence/absence of somatosensory evoked responses (SSEPs) post-injury. These variables were input to a regression model to predict final MPWS or epicenter white matter sparing. Results. Injuries > 20N peak force result in MPWS ≤ 5, single variable correlates to MPWS were: ($R^2 = 0.91$) for ultrasound measured lesion-size, ($R^2 = 0.82$) for final MPWS and white matter preservation. There is an increase in blood pressure and heart rate post-SCI but the correlation with the MPWS is poor ($R^2 < 0.2$). Other contributory variations are, differences in the diameter of cord and

sub-arachnoid spaces, contusion position relative to nerve roots, laminectomy size, temperature, and minor deviations of impact angles.

The percentage difference in preserved axons between those with and without weight supported locomotor recovery is narrow and there are inherent limits to control of variables that influence lesion severity.

Key words
axonal sparing, efficacy, hemodinamics, somatosensory evoked potential, spinal cord injury, ultrasound

D2-17

LONGITUDINAL PROFILE OF SENSORIMOTOR DEFICITS FOLLOWING SINGLE AND REPEATED PROJECTILE CONCUSSIVE INJURY (PCI)

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Mild traumatic brain injury (mTBI) is a significant concern for the civilian and military populations. Previously, we developed a device which produces a non-invasive projectile concussive impact (PCI) modeling mild close-head concussive injury in rats. This study evaluated the injury severity profile of sensorimotor dysfunction following single and repeated mTBI. Anesthetized rats were subjected to a single PCI injury (sPCI), repeated PCI (rPCI, 4 impacts, 1 h apart) or anesthesia (sham). Neurofunctional deficits were evaluated using the revised neurological severity scale (NSS-R), the rotarod test, and CatWalk gait analysis system. Results of NSS-R testing revealed significant neurological deficits in animals exposed to either single or repeated PCI at 1 h and 4 h post-injury ($p < 0.05$ vs. sham) that resolved by 24 h. Animals were tested for motor/balance abilities on an accelerated version of the rotarod task at acute (15 m, 1 h, 24 h) and subacute (7 and 14 d) post-injury time points. Rats exposed to a single PCI showed a trend towards worse performance at 15 m post-injury that resolved by 1 h post-injury. Animals exposed to repeated PCI showed significant motor deficits at 15 m (vs. sham) and 1 h post-injury (vs. sham and sPCI) that resolved by 24 h post-injury. Comprehensive gait analysis measurements were taken prior to injury (baseline) and at 2 h, 24 h, 72 h, 9 d and 28 d post-PCI. Animals exposed to a single PCI showed deficits on a limited number of dynamic gait walk parameters at 2 h post-injury that were resolved by 24 h post-PCI. In contrast, repeated PCI produced significant deficits across 28 separate parameters, the majority of which were sustained out to 72 h post-injury, but all of which resolved by 9 d post-PCI. Collectively, these results indicate that significant, albeit subtle, sensorimotor deficits are evident following a single PCI with more sustained deficits caused by repeated PCI. Further work is needed to evaluate the effects of repeated PCI exposures spaced at variable inter-injury intervals. Funded by CDMRP/DHP Grant W81XWH-12-2-0134.

Key words
gait analysis, mild TBI, motor/balance, neuropathology

D2-18

REPETITIVE MILD TRAUMATIC BRAIN INJURY MICE EXHIBIT STRUCTURAL AND HISTOPATHOLOGICAL ALTERATIONS AND LONG-TERM BEHAVIORAL CHANGES

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Mild traumatic brain injuries (TBI), alternatively referred to as concussions, are common in athletes, military personnel, and the elderly. Increasing evidence indicates that these injuries have long-term health effects. We developed a mouse model of repetitive closed head injury (rCHI), which closely mimics real life repetitive mTBI in human. Experimental brain injury was induced using a cortical impactor device mounted with a rubber coated metal tip, which is positioned centrally above the sagittal-suture midway. Mice were assessed at 1, 7, and 30 days post-injury for brain structural alteration with magnetic resonance imaging (MRI). To assess histological changes following m*TBI,* the glial fibrillary acidic protein (GFAP) and microglial Ionized calcium binding adaptor molecule 1 (Iba1) were monitored. Using a variety of cognitive and behavioral tests (rotarod, grip strength, Morris water maze (MWM), elevated plus maze and forced swimming test) we assessed the short- and long-term behavioral sequelae of rCHI. Our MRI results showed an initial lowering of apparent diffusion coefficient (ADC) values and a decrease in T_2 at 24 h after injury and no difference was observed by 30 days post-injury. Activated microglia (cortex) and astrocyte (hippocampus and corpus callosum) were observed from 7 post-injury, but no changed was found after 30 days post-injury. Significant impairments in motor deficits and neuromuscular function were observed 24 h post-injury, but no differences were found at 7 days post-injury. Significant differences were observed between the injured mice and the controls in both the elevated plus maze (day 30: $p < 0.05$; day 60: $p < 0.05$)) and forced swim test (day 60: $p < 0.05$), which showed a depression- and anxiety-like state in the injured mice. In MWM, animals received rCHI showed spatial learning and memory deficit when tested at 30 days after injury. Our results indicate that repetitive mTBI induces short-term brain structural and histological alterations as well as motor impairment, and profound and long-lasting learning and memory impairments, accompanied by a depression- and anxiety-like behaviors.

Key words
anxiety, cognitive function, depression, mild TBI, MRI

D2-19

CHARACTERIZATION OF CCI USING HIGH SPEED IMAGING

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Controlled cortical impact (CCI) is a widely used preclinical model for the study of traumatic brain injury (TBI). CCI has been employed to understand biomechanical and physiological mechanisms of TBI, behavioral responses, as well as to test potential therapeutic treatments. Recent discussion in the literature emphasizes the need for improved ''methods-reporting'' in preclinical research (Landis, et al., 2012 *Nature*, 490:187; McNutt, 2014 *Science*, 343:229). Two CCI impact actuators of the same model (Impact One, Leica) were used with a 3-mm impactor tip, 100 ms dwell time, and impact penetration depth controlled by changing the position of a stereotaxic frame. Poron® cushioning and a mouse brain with craniotomy were used to record CCI impactor tip with a high speed digital camera (Y3-S1, IDT Inc.). In the initial ~15ms after activation, the impactor tip makes two or three distinctive advances before it reaches the desired depth setting for full extension. In the 1st and 2nd advances, the tip extended ~50% and 80% of the targeted distance, indicating that a single activation results in three impact events. Impactor tip velocity on the 1st extension was normally faster than the preset values. The velocity of the tip on the subsequent extensions were significantly slower. Excluding

the movement of the tip for the first 15ms, then, the velocity of the tip was essentially identical regardless of velocity setting. The terminal location of the tip when it is stationary during final extension was near the desired depth for most of the impact time. The analysis suggests that velocity setting plays little, if any, role as a variable in CCI injury. Depth settings were reproducible and closely matched stereotaxic settings, suggesting this variable (as well as tip diameter and shape; not studied here) may be the significant factors in validation of CCI models. Results indicate CCI devices should be characterized to meet future ''methods-reporting'' standards.

Key words
calibration, controlled cortical impact, methods reporting

D2-20

DEVELOPMENT AND VALIDATION OF TWO ZEBRAFISH MODELS OF TBI

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Traumatic brain injury (TBI) is a leading cause of death and morbidity in industrialized countries with considerable associated direct and indirect healthcare costs. The cost and time associated with preclinical development of TBI therapeutics is lengthy and expensive. The Zebrafish (ZF) is an emerging model organism for studies of disease and development owing to its similarity in genome and cell signalling pathways in mammalian species, ease of genome manipulation, capacity for whole animal in vivo imaging, rapid rate of procreation, and amenability to large scale automated preclinical drug validation. We have developed a two-stage model of TBI in ZF using larvae and adult fish. In larval ZF, we developed a high-throughput method of screening therapeutic compounds in a chemically-induced brain injury model. As proof-of-concept, we demonstrate dose-dependent larval survival with known neuroprotective compounds (eg. MK-801). We are currently validating other known neuroprotective compounds in the larvae ZF model. Compound libraries of FDA-approved drugs are currently being screened for repurposing in our larval model. Candidate compounds will be further evaluated in an adult ZF model. We use a targeted 1-MHz pulsed high intensity focused ultrasound (pHIFU) system applied to adult ZF to produce a non-penetrating injury to the brain. Preliminary results indicate that pHIFU pressure amplitude at 10MPa results in a $70.5 \pm 1\%$ and $102 \pm 1\%$ change in NF160 expression at 5,000 and 10,000 cycles respectively. β-III tubulin shows a $14 \pm 1\%$ and $16 \pm 1\%$ increase at the same parameters. We also found a $30 \pm 1\%$ increase in cleaved caspase-3 expression in injured brains compared to controls. The adult ZF injury model allows whole animal behaviour outcome measures such as post-injury recovery times which demonstrate a dose dependent effect with increasing injury severity. Adult ZF subject to pHIFU also show locomotor swim deficits at 24 h post injury. Our preliminary results indicate that the ZF exhibits similar responses to injury and pharmacotherapeutic manipulation as found in mammalian pathophysiology after TBI. This suggests the possibility of using a two-step ZF injury model system to screen compound libraries to quickly identify potential therapeutic candidates at a fraction of the time and cost of studies in mammalian species.

Key words
drug screening, zebrafish

D2-21

COMPARISON OF TBI MODELS USING BRAIN DAMAGE MARKERS, AND HISTOLOGICAL AND BEHAVIORAL OUTCOMES IN OPERATION BRAIN TRAUMA THERAPY

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Successful preclinical testing of neuroprotective drugs depends on the selection and characterization of appropriate animal models. 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 animal models (parasagittal fluid percussion injury [FPI], controlled cortical impact [CCI] and penetrating ballistic-like brain injury [PBBI]). Here, we characterize/compare these models using circulating glial (glial fibrillary acidic protein [GFAP]) and neuronal (ubiquitin C-terminal hydrolase [UCH-L1]) markers, behavior, and histology.

At 4 h post-injury UCH-L1 was higher in CCI vs. FPI and PBBI ($P < 0.001$) and GFAP lower in PBBI vs. CCI and FPI ($P < 0.001$). Differences were also found comparing shams across models, with higher UCH-L1 levels in CCI vs. FPI and PBBI ($P < 0.001$) and lower GFAP levels in FPI vs. CCI and PBBI ($P < 0.001$ and $P < 0.01$, respectively). Increased cognitive deficits were observed in PBBI and CCI in the hidden platform task vs. FPI ($P < 0.001$) and in sham-CCI vs. sham-PBBI and sham-FPI ($P < 0.001$). Lesion volume was larger in PBBI vs. FPI and CCI ($P < 0.001$), while hemispheric volume loss was smaller in FPI vs. CCI and PBBI ($P < 0.001$). Average latency to find the hidden platform correlated with GFAP concentrations across models, but not with UCH-L1. Also, GFAP but not UCH-L1 correlated with lesion volume and hemispheric volume loss across models ($P < 0.001$).

Experimental TBI models display major differences in biomarker profiles and functional and pathological consequences. Circulating GFAP levels best reflected behavioral and histological outcomes. Our data provide a unique characterization of TBI models that enlighten our understanding of the relationship between biomarkers and traditional TBI outcomes and could advance translational research. Support: US Army W81XWH-10-1-0623

Key words
animal model, OBTT, traumatic brain injury

D2-22

CHARACTERIZATION OF A LABORATORY-BASED RODENT ROTATIONAL ACCELERATION TBI DEVICE

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A new experimental model was developed to induce TBI in rats through pure coronal plane angular acceleration to aid in the understanding of injury biomechanics and tolerance. Devices of this type can be large and have high maintenance costs. This project designed and characterized a compact rotational acceleration model to induce TBI in rodents through coronal plane rotational acceleration at specific magnitudes and durations. The design was based on the existing MCW Rotational Injury Device, consisting of an energy delivery device (EDD) and rodent helmet. The new EDD pneumatically propelled an impactor rod through a barrel using compressed air, towards the lateral extension of the existing helmet fixture. The helmet rotational axis was aligned with the cervical spine of the rat. When the impactor contacted the moment arm, the animal's head and helmet rotated in the coronal plane. The acceleration phase was designed to be much higher magnitude than the deceleration phase, so rodent TBI was attributed to the initial acceleration. The compact device delivered impactor exit velocities from the launcher of 8.1 ± 0.1m/s at input pressures of 12psi, and showed the potential for exit velocities as high as 14.7m/s at 35psi. These exit velocities, along with mass of the rod, allowed for a large amount of energy to be transferred to the helmet with only a 1.00x0.75x2.25-meter footprint (LxWxH). This will permit a wide range of rotational accelerations while maintaining consistent durations using the existing elastomer interface. These rotational accelerations were 560 ± 57krad/s^2, with a duration of 1.69 ± 0.24msec at input pressures of 12psi. The experimental methodology remains flexible, permitting adjustment of model parameters to continually expand the range of acceleration pulses to produce different TBI outcomes.

Key words
brain mass scaling, mild TBI, rodent model, rotational acceleration

D2-23

IN VS. OUT: CONTROVERSIES IN SHOCK TUBE BLAST EXPERIMENTS

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Inconsistencies in blast experiment methodologies confound the proper characterization of primary blast exposure. Comparisons across models of blast injury are virtually impossible due to non-standardized protocols. A major ambiguity is the placement of test subjects relative to the shock tube exit, interior vs exterior. This study characterizes overpressure waveform at potential test locations to determine ideal placements.

A cylindrical 305 mm diameter shock tube was used to generate blasts replicating those in the free field. Wave profiles and blast parameter measurements were acquired using specialized pressure transducer housing fixtures at various tube diameter (D_T) lengths from the exit. Finite element (FE) numerical simulations were used to validate experimentally derived blast parameter results.

FE simulations showed good comparison against experimental results. Shock waves were planar $8D_T$ lengths past the driver until $½D_T$ exterior. Significant decline of overpressure was found after $1D_T$ outside the shock tube. No significant differences in peak overpressure, duration, and impulse were found at the exit and $D_T/12$ past the shock tube exit.

Both inside and outside the shock tube are appropriate specimen placements depending on desired overpressure/duration parameters. Specimens should be placed at least 8–10 tube diameters downstream from the driver. Test subjects placed outside the shock tube should minimize standoff distance, ideally to less than half a tube diameter length. Findings can be scaled to cylindrical shock tubes of all sizes.

Key words
animal models, blast, numerical simulation, pressure profiles, shock tube, traumatic brain injury

D2-24

INFLUENCE OF HEAD ROTATIONAL ACCELERATION PULSE SHAPE ON BRAIN TISSUE STRAINS

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Brain tolerance to rotational acceleration is relevant for understanding injury thresholds and development of injury mitigation techniques for automobiles and sporting events. This computational-modeling study outlined effects of head rotational acceleration pulse shape on strains within brain tissues. A detailed finite element model of the human skull and brain was developed and validated previously. The model was exercised using realistic rotational accelerations with different magnitude and duration characteristics, and the principal strain response was extracted for parietal cortex, hippocampus, thalamus, and hypothalamus. Rotational acceleration magnitude was varied to three levels: 3.6krad/s^2 (M1), 5.3krad/s^2 (M2), and 6.6krad/s^2 (M3). Duration was varied to 9msec (D1), 18msec (D2), and 27msec (D3). Hippocampus and hypothalamus sustained more strain than cortex and thalamus. With increasing acceleration magnitude from M1 to M2 and M2 to M3, strain in all brain regions was uniformly increased by 42% and 80%. However, strains demonstrated regionally dependent changes with increasing duration (D1 to D3): 68%, 37%, 33% and 14% in parietal cortex, hippocampus, thalamus and hypothalamus, respectively. The trend was consistent for all acceleration magnitudes. This study demonstrated differing and independent effects of rotational acceleration magnitude and duration on strains within brain tissues during rotational acceleration. Magnitude has long been a correlate of injury severity and this study supports that finding in that increased acceleration magnitudes led to uniformly higher brain tissue strains (higher injury risk). However, rotational acceleration duration changed the strain distribution within the brain, resulting in different injury risks in different brain regions. This finding is significant as changing strain distribution with different durations can manifest as different injury distributions within the brain and different neuropsychological outcomes following exposure to head rotational acceleration.

Key words
finite element model, rotational acceleration, tissue strain, traumatic brain injury

D2-25

ELUCIDATING THE PATHOBIOLOGY OF IMPACT CONCUSSION IN A MOUSE MODEL OF MILD TRAUMATIC BRAIN INJURY

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We are investigating biomechanical and pathobiological determinants that link traumatic brain injury (TBI) with chronic traumatic encephalopathy (CTE), a tau protein neurodegenerative disease (McKee, 2013). We reported the first case series of postmortem brains from blast-exposed military veterans and compared results with brains from young athletes with histories of impact-induced concussive head injury (Goldstein, 2012). We found evidence of CTE neuropathology in the blast-exposed veterans that was indistinguishable from the neuropathology in the young athletes. Here we investigated concussive impact TBI using a new murine model deployed without anesthesia. The new model system accurately recapitulates biomechanical, pathophysiological, and clinical features of impact-induced TBI in humans. Our impact concussion mouse model: (1) prevents momentary impact-related skull deformation (crush injury) evaluated by two-axis high-speed videography, (2) induces acute lateralizing neurological signs (Boston University Concussion Scale, BUCS-3R) that resolve within 3 hours consistent with acute clinical concussion, (3) produces persistent neuropathological, neurochemical, and neurophysiological changes in the brain that recapitulate chronic effects of neurotrauma in humans. We used high-speed videography (capture rate: 10 μsec; 100 kHz) and kinematic analysis to show that this impact TBI model accurately replicates head kinematics observed in our blast TBI mouse model (Goldstein, 2012). Our results point to traumatic head acceleration as a major pathogenic contributor to acute and chronic effects of neurotrauma resulting from impact or blast TBI. These findings also provide insights into pathobiological responses following impact-induced concussion that may trigger chronic sequelae, including CTE.

Key words
traumatic brain injury

D2-26

CORRELATING MECHANICAL STRAIN AND BIOLOGICAL DAMAGE: AN *IN VIVO*, RODENT MODEL OF SPINAL CORD INJURY

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Rodent models of acute spinal cord injury (SCI) are often used to investigate the effects of injury mechanism, injury speed and cord force and displacement magnitude, on the ensuing cascade of biological damage in the cord. However, due to its small size, experimental observations have largely been limited to the gross response of the cord in SCI models. Therefore, the objective of this study was to determine mechanical strain patterns within the spinal cord during injury, in order to investigate the relationship between mechanical stimulus and biological damage in acute SCI. We developed and validated a novel MRI-compatible test apparatus to impose an acute, sustained (30 min.), cervical SCI in an *in vivo* rodent model, inside of a 7T MR scanner. Twenty-four rats (Sprague-Dawley, ~300g) underwent either a contusion (n = 12) or dislocation (n = 12) injury at the C5/6 level. Axial-slice MR image sets of the cervical spinal cord (C2-C8) were acquired at 'Pre-injury' and 'Sustained-injury' time points (resolution: 0.14x0.14x0.5mm). The two image sets were then registered, using a validated deformable registration algorithm. The registration yielded a three-dimensional displacement field that quantified the morphological change of the spinal cord due to injury, on a voxel-scale. Determining the spatial derivatives of the displacement field facilitated the calculation of mechanical strain (in 3D) throughout the cervical spinal cord. The spinal cords were harvested, sliced axially, and stained with NeuN to measure neuronal viability in the ventral horns of the gray matter, after injury. A correlation analysis was performed to determine how the NeuN data correlated with the mechanical strain measured in the ventral horns, over a region of +/- 3mm, rostro-caudal, from the injury epicenter.

Key words
acute SCI, mechanical strain, spinal cord morphology

D2-27

CHALLENGES IN ASSESSING TAU IN A LARGE ANIMAL MODEL OF TRAUMATIC BRAIN INJURY

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The tauopathies are a heterogeneous group of neurologic diseases characterized by abnormally aggregated tau protein. Head injury is considered an important potential cause of tauopathy, yet the mechanism of tau accumulation following injury is poorly understood. Most work to date has been in rodent models. It is unclear if the immature brain is selectively vulnerable to tauopathy after injury, and the putative timeframe for pathologic tau accumulation after injury is poorly defined. We evaluated hyperphosphorylated tau in a large animal model with short survival times following cortical impact. We describe the challenges in validating tau in this model.

Sixteen immature swine underwent scaled focal cortical impact using a well-characterized contusion model. Animals were 5 days, 1 month or 4 months old at injury. Survival times were 1 week or 1 month. A protocol for peroxidase immunohistochemistry was optimized for paraffin embedded tissue using antibody to hyperphosphorylated tau (AT8). Multiple whole-brain coronal slices were evaluated at the injury site. Positive controls included human brain with Alzheimer disease and tissue from a pig model of diffuse brain injury previously published with tau positivity. Negative and sham controls were also used. Blinded evaluation of a single case was performed by 4 neuropathologists.

Hyperphosphorylated tau was detected in axonal swellings in one subject. Other subjects had focal or multifocal staining of neurons, glia or neurites that was equivocally positive and difficult to interpret. Review of a single blinded case by 4 neuropathologists yielded low inter-rater reliability (50% agreement). Alternate methods to interrogate brain tissue for abnormal tau in this model are in progress

Hyperphosphorylated tau positivity has not been unequivocally demonstrated or excluded in any subjects to date. These results reflect the challenge in validating tau for a large animal model with limited species-specific positive controls and highlights the need for caution, and additional confirmatory measures before reaching unequivocal conclusions regarding the pathophysiology of trauma and tauopathy in immaturity and across species.

Key words
immaturity, large animal model, tauopathy, TBI

D2-28

COMPUTATIONAL INVESTIGATION OF BRAIN NEUROTRAUMA BIOMECHANICS UNDER BLAST

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Due to moral and technical limitations for experimental studies on blast-induced traumatic brain injury, computational methods such as finite element (FE) analysis serve as the most common tools in the engineering sciences to study the biomechanics of brain neurotrauma. In this research, a numerical study was carried out on the interaction of blast shockwaves with the head. The tissue level parameters such as shear stress, shear strain, and intracranial pressure (ICP) as well as the kinematic parameters such as linear acceleration of brain were recorded to provide an evaluation of injury related parameters. Due to the structural inhomogeneity of the human head as well as different tolerances and functions of head components, the head response to blast waves can differ with respect to the impact location of shockwaves on the head. Accordingly, four different blast scenarios were performed based on the approaching blast waves from the front, back, top, and side of the head to highlight the effect of blast directionality on the head response. A detailed validated FE head model including most anatomical features of the human head was employed. Ls-Dyna, a nonlinear explicit FE solver was used to carry out all simulations. In order to comply with the lung injury threshold, a 520 kPa blast overpressure was generated around the head. The primary results showed the development of peak ICP and shear stress values inside the brain mainly at the coup site, the parietal lobe, and the brainstem. However, a comparison of brain biomechanics at different directions revealed that the side blast produced the highest peak values for both tissue and kinematic parameters, hence imposing higher risks of neurotrauma. However, while kinematical responses are addressed as main injury predictors in most studies, our correlational analysis did not indicate a direct relationship between tissue and kinematic parameters for all directions. Hence, the tissue level parameters were ascertained as a more reliable injury criterion. The observations from the present study may be considered in the design of protective headgears.

Key words
blast induced neurotrauma, computational biomechanics, directionality, finite element analysis, tissue level parameters, traumatic brain injury

D2-29

EFFECT OF SPACE CONFINEMENT ON THE LEVEL OF BLAST INDUCED TRAUMATIC BRAIN INJURY

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Blast-induced assaults to the head can impose traumatic injuries to the head brain. Parameters such as the intensity of blast and the media significantly influence the level of brain neurotrauma. Severe blast scenarios are expected in confined spaces. According to some observations, the rate of fatality and morbidity in confined spaces has shown a significant increase compared to similar open-space blast scenarios. The aim of this study is to examine the influence of confinement on different injury-related biomechanical parameters such as the brain intracranial pressure (ICP), shear stress, and strain. Investigations are conducted on a 50^{th} percentile finite element human head model exposed to blast at different locations in a confined space. The head model employed in this study consisted of essential components for accurate computational analysis and has been validated against cadaveric experiments. The results of the investigations indicate that in such complex environments, besides the direct blast wave incidents similar those in open spaces, human head would also experience reflection waves from the surrounding walls. Such reflected waves extend a longer duration of load which intensifies the level of brain injury. Additionally, for the locations close to walls where the magnitudes of the reflected waves from neighboring wall are the highest, the peak values of ICP and shear stress of the brain are drastically amplified. It is concluded that the duration and magnitude of reflected waves applied on the human head could be several times larger when the head is placed at the corners of the confined space. While the brain is prone to traumatic injuries in confined spaces the severity and fatality of blast-induced trauma would remarkably be elevated when the head is located near the walls and particularly at the corners.

Key words
biomechanical parameters, blast injury, blast media, computational biomechanics, confined space, finite element analysis

D2-30

LIMITED EVIDENCE OF BRAIN INJURY IN RATS EXPOSED TO EXPLOSIVE-DRIVEN PRIMARY BLAST

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Explosive blast has been a major cause of brain injury in recent war theaters. Blast can cause injury by different mechanisms, but the specific contribution of shock wave transmission across tissues, (''primary'' mechanism of injury by blast) is still unclear. We explored the neurobehavioral and neuropathological outcome in anesthetized and restrained rats exposed to explosive-generated blast waves, under conditions aimed to minimize non primary mechanisms of injury. The outcome was evaluated across a range of peak blast overpressures and pulse durations, at different angles of exposure, in the presence and absence of chest protection. Results suggest very mild levels of brain injury even at blast intensities approaching thresholds of lung injury-related lethality, both in the absence (21 psi) and presence of torso protection (50 psi). Neurological scores, motor coordination, spatial learning, parameters of anxiety were not affected. Loss of startle response was most likely

due to hearing impairment. Histopathological evidence was overall mild, with presence of scattered blast intensity-dependent intracranial microhemorrhages. The most striking pathological feature was dose-dependent FD neurosilver and Fluorjade B staining of the superior colliculus, with some evidence of astroglia and microglia activation in the same areas. Molecular evaluations showed evidence of a mild increase in levels of spectrin breakdown products, suggestive of calpain activation, and of several cytokines both in frontal cortex and hippocampus. Levels of neuron specific enolase and brain-derived neurotrophic factor, were increased in plasma after blast exposure. Overall, a single blast exposure did not appear to cause more than mild evidence of brain injury in rat, with maximum impact on neurosensory structures and pathways.

Key words
primary blast, rat, TBI

D2-31

ROLE OF THE CONTRALESIONAL CORTEX IN FORELIMB RECOVERY AFTER EXPERIMENTAL TBI

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Deficits in sensorimotor function after clinical TBI are a significant problem with up to 30% of patients experiencing chronic impairment. Previously, we have shown that left-lateralized controlled cortical impact (CCI) injury in the rat sensorimotor cortex induces a trans-hemispheric shift in affected, right forelimb-evoked fMRI cortical activation over to the homotopic, contralesional cortex (CLCx). While spontaneous recovery of affected limb-use occurs in this model, it is unclear whether CLCX-shifted activation is an indicator of beneficial map plasticity or if this is maladaptive. In order to determine if the CLCx plays a functional role during post-injury recovery of limb-use, forelimb-reaching was tested before and during temporary silencing of the CLCx using intraparenchymal muscimol injection (versus vehicle, n = X/group) and this was performed longitudinally at 1 and 4 weeks after CCI injury in the adult rat. The results showed that at 1 week post-injury and before silencing, TBI-affected forelimb-reaching was reduced by 71% from pre-injury levels as expected from prior work ($P < 0.05$). Silencing the CLCx 1 day later resulted in deficits in the TBI-unaffected limb compared to pre-silencing levels ($P < 0.05$), simply indicating a correctly targeted cortical injection. In addition however, there was a complete reversal of the TBI-affected limb-reaching deficits to pre-injury levels ($P < 0.05$) indicating significant involvement of the CLCx in TBI-affected limb function acutely post-injury. By 4 wks post-injury, deficits in TBI-affected forelimb-reaching measured before a second period of silencing had spontaneously recovered to within 20% of pre-injury levels ($P > 0.05$). Although CLCx silencing one day later induced deficits in the TBI-unaffected limb as expected ($P < 0.01$), opposite to 1wk post-injury, TBI-affected-limb function was also significantly reduced to 32% of pre-injury levels (45% of pre-silencing, $P < 0.05$). This indicates that prior fMRI data showing an ipsilesional-to-CLCx-shift in activation likely underpins affected forelimb function chronically. The absence of any new ipsilesional regions of cortical fMRI activation during CLCx silencing further indicates the importance of the CLCx to affected limb function. Support: UCLA BIRC

Key words
cortical silencing, fMRI, neuroplasticity, staircase reaching task

D2-32

FINITE ELEMENT SIMULATION OF BRAIN DEFORMATION FROM SIX DEGREE OF FREEDOM ACCELERATION MEASUREMENTS OF MILD TRAUMATIC BRAIN INJURY

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Human mTBI biomechanics are complex and poorly understood, rendering screening efforts ineffective. Inertial rotation and translation are thought to cause diffuse brain trauma, but human tolerance to acceleration in all rotational and translational directions (six degrees of freedom, 6DOF) has not been measured for a human injury. Using novel instrumented mouthguards that rigidly couple to the upper dentition, we measured head collision biomechanics in full 6DOF, including the first complete measurements of human mTBI. Over 500 collisions among 31 subjects were measured at American football, boxing, and mixed martial arts events. Two subjects sustained a concussion during competitive play: one suffered loss of consciousness (LOC) while the other self-reported more subtle post-concussive symptoms, including headache, impaired concentration, and slowed reaction. Using the KTH finite element (FE) model, we mapped complex spatiotemporal kinematics measured in vivo onto the brain's anatomy. The LOC injury reported the highest principal strain (50%) among 50 randomly-selected non-injury collisions and the self-reported injury. Six non-injury collisions produced higher strains than the self-reported injury (18%), but in different anatomical regions. Maximum strain in both injuries occurred in the corpus callosum, and no non-injuries reached injury strain levels in this region. The LOC injury also predicted large strains in the brainstem. Our 6DOF measurement system predicted deformation in brain structures consistent with observed neurological deficits. Injury and non-injury collisions were distinguished by the severity and location of maximum tissue strain. Damage to the corpus callosum has been shown to disrupt interhemispheric communication and affect perception, while damage to the brainstem has been shown to induce LOC. While more data is required to characterize brain tissue mechanics across a wider spectrum of injuries, congruity between our measured kinematics, predicted tissue deformations, and observed symptoms indicates the promise of this system as a clinical tool.

Key words
biomechanics, finite element modeling, mild traumatic brain injury (mTBI), screening, sensors, sports concussion

D2-33

ANXIETY-LIKE BEHAVIOR IN MICE AFTER TRAUMATIC BRAIN INJURY: DISCUSSION AND COMPARISON OF COMMONLY-USED TESTS AND MEASUREMENTS

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Traumatic brain injury (TBI) survivors often exhibit long-term symptoms of anxiety, and anxiety-like behaviors in animal TBI models are a common functional measure. However, anxiety measures in experiments in brain-injured rodents have yielded variable results.

Some studies have concluded that TBI results in anxiety, other reports indicate no change, while others state that TBI decreases anxiety-like states resulting in ''risk-taking'' behaviors. Differences in species/strain of animal, experimental model and severity of TBI, time of testing post-injury, testing conditions and criteria may obviously contribute to the variability in conclusions. We investigated the relationships between commonly-reported variables in the open field (OF) and elevated zero maze (EZM) that are employed to draw conclusions regarding anxiety-like states in rodents after TBI. Male mice (C57BL6/J) that sustained TBI by controlled cortical impact (CCI) were tested at multiple times post-injury in the OF and EZM. In both injured and sham-operated animals coefficients of determination were very low for time spent in the center of the OF and time in the open quadrants of the EZM; commonly used measures of anxiety, suggesting that the variability in these measures is largely unshared and likely accounted for by other variables. Furthermore, correlations between time spent in the center zone of the OF and time spent in open quadrants of the EZM were greater when the animals were tested for 60 minutes, suggesting that testing for shorter durations of time represents behavior specific to habituation to the environment and may not accurately represent exploratory and anxiety-like behaviors that result from longer periods of testing. These results demonstrate the difficulty of comparing the results of behavioral testing from rodent TBI experiments, particularly when the studies employ different apparatus and report different dependent measures.

Key words
animal testing, anxiety, behavior

D2-34

METABOLITE, HISTOPATHOLOGICAL AND FUNCTIONAL CHANGES IN THE HIPPOCAMPUS AFTER BLAST EXPOSURE

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Almost 80% of blast induced TBI cases reported in the military were of mild severity where soldiers presented no external signs of injury but whose brain may have been damaged and presented symptoms of cognitive, physical and neuropsychiatric dysfunctions. This study aims to investigate the effect of blast exposure and how it affects on hippocampal function and memory.

Briefly, male Sprague Dawley rats were exposed to a single blast at $\sim$180kPa. The animal were evaluated before and after the injury on the radial arm maze and subjected to longitudinal Single Voxel Spectroscopy (SVS) ^{1}H-MRS imaging using PRESS technique (voxel size of $3.5\times2\times3.5\,mm^3$) in the hippocampus. In addition, TUNEL assay for apoptotic neurons and NeuN immunohistochemistry was carried out on brain slices at -3.8 mm bregma at stipulated post-blast sacrifice timepoints (Day 1, Day 3, Day 5, Day 14, and Day 28 post-blast).

In the hippocampus, there was a slight increase in TUNEL-immunoreactivity and the NeuN immunostaining showed shrunken and distorted neurons at 24 h and 72 h after blast injury, which may be indicative of either ischemic or physical injury. Transient memory impairments in the radial arm maze were detected at day 4 and 5 after blast injury. NAA metabolite level assessed by ^{1}H-MRS was also decreased at day 3 after blast injury which mirrors the decrease in other CNS pathological conditions involving neuronal loss or dysfunction such as Alzheimer's disease and stroke. A decrease in hippocampal glucose was observed in the ^{1}H-MRS spectrum at 3 days post-injury which points towards a depressed CNS metabolism. Overall, histopathological changes in the hippocampus coincide with the transient functional changes after blast exposure.

Key words
behavioral changes, blast injury, H-MRS imaging, hippocampus damages, metabolite changes

D2-35

CONTROLLED-CORTICAL IMPACT REDUCES RATS' ABILITY TO SUSTAIN APPLICATION OF SUBMAXIMAL FORCE

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Traumatic brain injury (TBI) is an increasingly large health risk in the United States and often results in a severe lack of motor control and weakness. We have recently reported that experimental TBI in rats induces a chronic impairment in maximal volitional forelimb strength. Many activities of daily living, however, require consistent application of controlled submaximal force rather than maximal force. Therefore, we sought to investigate the effect of a controlled-cortical impact (CCI) on rats' ability to generate a submaximal level of force over a sustained duration. Rats were trained using the isometric force task to sustain a pull of at least 35 grams over 1 second in length. After achieving proficiency at the task, rats' received a CCI in motor cortex contralateral to the trained limb and underwent 6 weeks of post-lesion assessment. Preliminary results indicate that CCI results in chronic deficits in rats' ability to sustain submaximal force thresholds. These results further characterize motor impairments resulting from CCI and may provide an additional model in which to test future therapies to enhance recovery from TBI.

Key words
controlled cortical impact, isometric force task, sustained force, TBI

D2-36

NEUROPATHOLOGICAL AND BIOCHEMICAL ASSESSMENT OF CHIMERA: A NOVEL CLOSED-HEAD IMPACT MODEL OF ENGINEERED ROTATIONAL ACCELERATION

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Despite promising outcomes from many preclinical studies, clinical studies have failed to identify effective pharmacological therapies for traumatic brain injury (TBI), suggesting that the translational potential of preclinical models requires improvement. To address the challenge of generating a simple and reliable model of rodent TBI, we have developed a novel neurotrauma model called CHIMERA (Closed-Head Impact Model of Engineered Rotational Acceleration) that fully integrates biomechanical, behavioral, and neuropathological analyses.

CHIMERA is distinct from existing rodent neurotrauma models in that it uses a completely non-surgical procedure to precisely deliver impacts of defined dynamic characteristics to intact animal head while allowing unconstrained head movement.

In this study we characterized the acute neuropathological and biochemical outcomes of repeated TBI (rTBI) in mice using CHIMERA.

Male, wild-type mice were subjected to two closed-head impacts spaced at 24 h. Microglial response was assessed by Iba-1 immunohistochemistry while axonal injury was assessed by silver staining at 48 h post-rTBI. Protein levels of TNFα and IL-1β were measured at 6, 12 and 48 h post-rTBI using ELISA. Endogenous total and phosphorylated tau levels were assessed at 6, 12 and 48 h post-rTBI using Western blotting.

Injured brains showed significant widespread microglial activation in white matter as well as diffuse axonal injury (DAI) at 48 h post-rTBI. Protein levels of TNFα and IL-1β showed $\sim$1.7- and 2-fold increase, respectively at 48 h following rTBI. Injured brains also showed $\sim$1.5 to 3.5-fold increase in the levels of phosphorylated tau protein, peaking at 12 h following rTBI.

CHIMERA is a simple and reliable model of murine TBI that replicates several aspects of human TBI such as neuroinflammation, DAI as well as tau hyperphosphorylation.

Key words
microglial activation, muse closed-head injury model, tau phosphorylation

D2-37

BIOMECHANICAL AND FUNCTIONAL CHARACTERIZATION OF CHIMERA: A NOVEL CLOSED-HEAD IMPACT MODEL OF ENGINEERED ROTATIONAL ACCELERATION

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Traumatic brain injury (TBI) is a leading cause of death and disabilities. A major challenge in TBI research is that many common experimental models do not faithfully replicate the biomechanical aspects of TBI in real-life. To address this issue, we have developed a novel rodent TBI model with high precision, reliability and translatability, called CHIMERA (Closed-Head Impact Model of Engineered Rotational Acceleration). It is distinct from existing models in that it delivers precise impact to the intact head in a non-surgical procedure, and allows unrestrained head movement.

In this study we characterized the biomechanical and acute functional outcomes of repetitive TBI using CHIMERA.

Two TBI at 0.5 J impact energy were induced to adult C57Bl/6 mice at 24 h apart. Head kinematics were assessed using high-speed videography (5000 fps). Post-injury neurological outcomes, motor function, and anxiety-like behavior were assessed by loss of righting reflex duration (immediately post-injury), neurological severity score (1 h, 24 h, 48 h), falling latency from accelerating Rotarod (24 h, 48 h) and open-field thigmotaxis (24 h), respectively.

Head kinematic analysis showed a peak linear displacement of 49.6 ± 3.5 mm, and a peak angular deflection of 2.6 ± 0.28 rad. Peak linear and angular velocities were 6.6 ± 0.8 m/s and 305.8 ± 73.7 rad/s, respectively. The head experienced peak linear and angular accelerations of 385.1 ± 52 g and 253.6 ± 69.0 krad/s^2, respectively. Injured mice showed significantly prolonged loss of righting reflex, displayed neurological and motor deficits, and anxiety-like behavior. CHIMERA is a simple, reliable model of TBI that offers integration of biomechanics and functional assessment.

Key words
behavior study, biomechanics, head kinematics, mouse closed-head injury model

D2-38

LONGITUDINAL EVALUATION OF HISTOLOGICAL AND NEUROBEHAVIORAL CHANGES IN A MOUSE MODEL OF R-MTBI: A FOLLOW UP AT 2 YEARS POST INJURY

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The mechanisms contributing to TBI-induced neurodegeneration are unknown and few studies have investigated the long-term impact of mTBI on neurobehavioral outcome.

Animals were subjected to a single exposure of anesthesia, repeated anesthetic exposure, a single closed head injury, or 5 repetitive injuries, 1 every 48 hours (r-mTBI). Cognitive function was evaluated at 24 months postinjury/anesthesia using the Barnes maze. Sections were stained with LFB/CV using standard histological protocols. Sets of adjacent sections were stained for GFAP, Iba-1, CD45, APP and a panel of various tau antibodies. For tau biochemistry, tissue homogenates were coded and sent to Dr. Davies for blinded quantitative assessments.

Consistent with our earlier observations, the performances in the Barnes maze of the sham and s-mTBI were similar, while the cumulative distance to the target hole for the r-mTBI was approximately twice that of the other groups. Continuing white matter degradation accompanied by a significant increase in levels of GFAP, Iba1, and CD45 was observed in the corpus callosum of the animals exposed to r-mTBI. No change in soluble cortical/hippocampal Tau was observed between injured or sham animals at 24 months post injury.

These data provide evidence that, whilst a single mTBI produces a clinical syndrome which remains static in the period following injury, repetitive injuries produce behavioral changes that continue to evolve many months after the initial trauma. Neither single nor repetitive mTBI were associated with elevated brain levels of abnormal tau phosphorylation at 24 months post mTBI. In this model, progressive neuroinflammation rather than tau pathology appear to be the driving factor and contribute to the neurobehavioral deficits observed.

Key words
behavior, repetitive mild TBI, tau

JOURNAL OF NEUROTRAUMA 31:A-127–A- (June 15, 2014)

DOI: 10.1089/neu.2014.9934.abstracts

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