

ALTERATIONS OF FUNCTIONAL PROPERTIES OF HIPPOCAMPAL NETWORKS
FOLLOWING REPETITIVE CLOSED-HEAD INJURY

by

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Thesis submitted to the Faculty of the
Neuroscience Graduate Program
Uniformed Services University of the Health Sciences
In partial fulfillment of the requirements for the degree of
Doctor of Philosophy 2014



UNIFORMED SERVICES UNIVERSITY, SCHOOL OF MEDICINE GRADUATE PROGRAMS
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FINAL EXAMINATION/PRIVATE DEFENSE FOR THE DEGREE OF DOCTOR OF PHILOSOPHY
IN THE NEUROSCIENCE GRADUATE PROGRAM

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Date of Examination: October 24, 2014

Time: 1:00pm

Place: B2090

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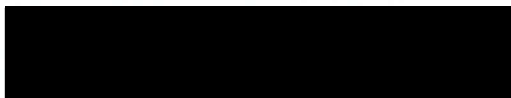


DISSERTATION APPROVAL FOR THE DOCTORAL DISSERTATION IN THE NEUROSCIENCE
GRADUATE PROGRAM

Title of Dissertation: "ALTERATIONS OF FUNCTIONAL PROPERTIES OF HIPPOCAMPAL
NETWORKS FOLLOWING REPETITIVE CLOSED-HEAD INJURY"

Name of Candidate: Omar Logue
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ACKNOWLEDGMENTS

The successful completion of this thesis project is the direct result of the education, mentoring, training, and generosity that I have received from the faculty and staff at USUHS. Their collective matrix of support is far more responsible for the fulfillment of all requirements for graduation than all of my own individual efforts. I wish to recognize and humbly thank the following individuals for their time and energies from which I have greatly benefitted.

I am deeply grateful for the generosity of Dr. Neil Grunberg , Dr. Ranjana Verma, and Ms. Xiufen Xu for sharing their behavioral data from their single and triple closed-head injury behavioral studies.

Thanks also to Ms. Xiufen Xu, Research Assistant in the Galdzicki laboratory. Your technical expertise in performing the closed-head injury surgeries, meticulous attention to the animal husbandry, and unwavering maintenance to the inventory of all laboratory supplies, and reagents is greatly appreciated.

To Dr. Eleanor S. Metcalf, former Associate Dean of Graduate Education, thank you for creating and sustaining a nurturing environment that enabled me to learn, progress, and grow during my education at USUHS. You are a tireless advocate for all of us.

To Dr. Gregory P. Mueller, Vice-Chair of Research and Acting Associate Dean of Graduate Education, thank you for the training and mentoring I received during my first-year rotation in your lab as I studied the synthesis of oleamide in blood. Thank you also for your support and feedback that has been invaluable during the final months of completion of this thesis.

To Dr. Kristin Heitman, Assistant Professor, Department of Military History at USUHS, I thank you for your one-on-one tutoring sessions on scientific writing. You taught me how to implement writing strategies such as a Context of Justification, and an Objection-and-Reply. Furthermore, you trained me to utilize the literature from previous publications to not only bolster my own data, but more importantly to adequately address the concerns and objections of any critical reader. Thank you as well for your guidance on how to manage the universal experiences that every graduate student faces when earning a Ph.D.

Thank you to Dr. David J. Mears for agreeing to serve as Chair of my Thesis Committee. The Clinical Head and Neck/Functional Neuroscience course that you direct is not only my favorite graduate school course, but it also serves as the bedrock foundation for all other subfields of neuroscience that I will study in the future. I am grateful for your guidance, feedback, and critical analysis of my data and writing.

My appreciation goes to Dr. Suzanne B. Bausch for your uncompromising adherence to and enforcement of the high standards of electrophysiology. You have been one of the toughest instructors that I have faced at USUHS, and that is precisely why I wanted you to serve on my Thesis Committee. Thank you also for the instruction I received from the Neuropharmacology course. While the Clinical Head and Neck/Functional Neuroscience course taught me how to localize a lesion in the central nervous system, the Neuropharmacology course trained me how to pharmacologically treat the neurological deficits caused by the lesion.

To Dr. Sharon L. Juliano, I am much obliged for all of your advocacy, understanding, and moral support that you have provided throughout this thesis project. I

would have never made it to this stage without your efforts as the Neuroscience Program Chair to facilitate my progress through each stage of my education at USUHS.

Thank you to Dr. Richard J. Siarey for my initial training in field potential recordings, creating viable hippocampal slices, and troubleshooting the rig failures that will invariably occur at the most inopportune times. Without your training, I would have never been able to generate our most important discovery of enhanced LTP one week after a triple closed-head injury.

My deep thanks go to Dr. Nathan P. Cramer for your instruction in whole-cell patch clamping, data analysis, and data interpretation. Your patience, encyclopedic knowledge of electrophysiology, and natural teaching ability were all instrumental in my gaining proficiency in voltage-clamp and current-clamp recordings. Thank you for designing and writing data analysis programs using IGOR analytical software. I seriously doubt that I would have been able to tease out any statistical differences without you generously allowing me to use your analytical programs.

It is not possible to adequately thank my thesis advisor, Dr. Zygmunt Galdzicki. An eternal optimist, Dr. Galdzicki had faith and resoluteness in my nascent abilities long before I ever believed in myself. Dr. Galdzicki has demonstrated a tremendous degree of flexibility, understanding, and resourcefulness in guiding me through this thesis project. His acceptance of any situation, regardless of how much doubt and uncertainty that may exist, instilled the confidence in me that the answers to our scientific questions would eventually reveal themselves. He welcomes and looks forward to with anticipation the generation of new questions when we reach conclusions to our initial questions. From day one, Dr. Galdzicki has reminded me that education is not a linear process, where “X”

hours of work, will yield a proportional degree of productivity and success. Year after year, he would remind me that acquiring expertise in designing experiments, technical proficiency, critical thinking, data analysis and interpretation, grant writing, and the ability to formulate new questions from our data and results will slowly come as I approach the conclusion of a research project.

To be sure, I have many more years of postdoctoral training to undergo before I can honestly claim to have mastery of the above stated areas of neuroscience. However, the progress that I have made thus far is only from the mentoring that I have received from these twelve researchers, especially Dr. Galdzicki. Please accept my heartfelt thanks and deep gratitude to all of you.

DEDICATION

This thesis is dedicated to the memory of my maternal grandmother, Mrs. Latifie Farris Nicola, and to my father, Mr. Francis Marion “Frank” Logue III. They both succumbed to the complications of Parkinson’s disease.

As this thesis is concluded, I now understand how naïve I was at the beginning of graduate school. I have gained an appreciation for the complexity of the almost insurmountable challenges clinicians and basic science researchers must confront when treating and attempting to cure neurological disorders.

It is my hope that I will one day gain the ability to make a valuable contribution to a laboratory dedicated to developing novel and efficacious treatments and therapies for neurological diseases and disorders.

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October 2014

ABSTRACT

Alterations of Functional Properties of Hippocampal Networks Following REPETITIVE Closed-Head Injury

Omar Logue, Doctorate in Philosophy, 2014

Thesis directed by: Dr. Zygmunt Galdzicki, Professor, Department of Anatomy, Physiology, and Genetics

Traumatic brain injury (TBI) is the leading cause of death for persons under the age of 45. Military Servicemembers who have served on multiple combat deployments, and contact-sport athletes, are at particular risk of sustaining repetitive TBI (rTBI). Cognitive and behavioral deficits resulting from rTBI are well documented. Optimal associative long-term potentiation (LTP), occurring in the CA1 hippocampal Schaffer collateral pathway, is required for both memory formation and retrieval. Utilizing our mouse model of rTBI, we hypothesized that a triple closed-head injury (3X CHI) will trigger alterations in hippocampal function to include inhibition of LTP and attenuation of electrical activity. One week after 3X CHI, extracellular recordings were performed to evoke Schaffer collateral LTP in the CA1 area. Surprisingly, ipsilateral CA1 LTP was enhanced in mice from the 3X CHI treatment group. The intrinsic properties of CA1 neurons were evaluated with whole-cell patch-clamp recordings. 3X CHI ipsilateral CA1 neurons exhibited significant increases in action potential amplitude, maximum rise slope, and maximum decay slope, while the action potential was decreased. Recordings of CA1 neuron postsynaptic currents were conducted to detect spontaneous excitatory (EPSCs) and inhibitory (IPSCs) and respective miniature currents (mEPSCs and mIPSCs). In the 3X CHI mice, the sEPSCs and sIPSCs of ipsilateral CA1 neurons had an

increased frequency of events but decreased peak amplitudes. Conversely, 3X CHI altered the action potential-independent miniature postsynaptic currents in a different manner. The mEPSCs of ipsilateral CA1 neurons displayed both an increased frequency of events and larger peak amplitudes. Moreover, the effect of 3X CHI on mIPSCs was opposite to that of the sIPSCs. That is, the frequency of events in the mIPSCs was decreased, while the peak amplitudes were increased. These results, which are contrary to our original hypothesis, are consistent with a mechanism in which repetitive closed-head injury may affect CA1 hippocampal function by promoting a shift between excitatory and inhibitory synaptic inputs.

TABLE OF CONTENTS

LIST OF TABLES	xiv
LIST OF FIGURES	xv
CHAPTER One: Introduction.....	16
Mild traumatic brain injury: epidemiology and differential diagnosis	16
Repetitive traumatic brain injury (rTBI): Pathophysiology.....	19
Second-Impact Syndrome: A Subcategory of rTBI Pathophysiology	20
Postconcussion Syndrome (PCS): Persisting Symptoms and Poor Outcome.....	21
Subconcussion: The Undetected Contributor of rTBI Progression and Pathology ..	22
Chronic Traumatic Encephalopathy: The Hallmark Pathology of rTBI.....	24
rTBI Patients That Present with Neurological Deficits with an Absence of	
Postmortem CTE Pathology	26
The Relationship Between rTBI, CTE, and Posttraumatic Stress Disorder (PTSD)	27
Human Electrophysiological Manifestations of rTBI: The P300 Event Related	
Potential	28
Hippocampal-Dependent Memory and the Role of Area CA1 in Long-Term	
Potentiation	30
Vulnerability of the Hippocampus to Repetitive TBI.....	32
Animal Models of Repetitive TBI	33
Histopathological Effects and Neurobehavioral Deficits of rTBI	34
Histopathological Effects of rTBI	34
Cognitive and Behavioral Deficits Associated with rTBI.....	35
Electrophysiological Studies of Single TBI in Hippocampus	36
Single TBI Studies That Demonstrate Increased Hippocampal Excitability ...	37
Single TBI Studies That Demonstrate Decreased Hippocampal Excitability ..	37
Rationale and Hypothesis	39
CHAPTER Two: Triple Closed-Head Injury (3X CHI) Model of Repetitive TBI (rTBI)42	
Key Elements of the Experimental Design of rTBI.....	42
Rationale for Using Closed-Head Injury to Model rTBI	42
Method for Closed-Head Injury Surgery	43
Experimental Design of Overall rTBIs Study.....	44
CHAPTER Three: Extracellular Field Potential Recordings (LTP/PPF).....	48
Rationale	48
Methods for assessment of Paired-Pulse Facilitation (PPF) of Schaffer collateral-CA1	
synapses and Long-Term Potentiation (LTP) experiments in the CA1 area of the	
hippocampus	48
Results of Paired-Pulse Facilitation of Schaffer Collaterals Synapses	51
Results of Long-Term Potentiation in the Area CA1 of Hippocampus.....	52

CHAPTER Four: The Impact of rTBI on Intrinsic Membrane Properties in CA1 Pyramidal Neurons.....	54
Rationale	54
Slice Preparation	54
Electrophysiology	55
Results of Intrinsic Membrane Properties Experiments	56
CHAPTER Five: rTBI Affects the Network Properties in Area CA1 of the Hippocampus	58
Rationale	58
Slice Preparation	58
Electrophysiological Recordings	59
Results of the spontaneous excitatory postsynaptic current experiments	60
Results of the Miniature Excitatory Postsynaptic Currents Experiments.....	61
Results of the Spontaneous Inhibitory Postsynaptic Current Experiments	62
Results of the Miniature Inhibitory Postsynaptic Currents Experiments.....	63
CHAPTER Six: Discussion	65
Novelty of Results.....	65
Experimental Design and its Relevance for Modeling rTBI	66
rTBI Causes Changes in CA1 Hippocampal Function	68
Enhanced LTP Does Not Correlate with a Recovery of Function.....	70
Differential Regulation of the Subunits of Glutamatergic and GABAergic Receptors: A Possible Mechanism for rTBI-induced changes in hippocampal circuitry	73
AMPA Subunit Composition Determines Its Biophysics and Kinetics	73
Subunit Composition, Location, and Kinetics of AMPARs on CA1 Pyramidal Neurons	74
Tumor Necrosis Factor-Alpha (TNF α): Cytokine with Synaptic Plasticity Actions That Are Dependent Upon Receptor Type	78
Differential Regulation of Ionotropic Receptor Subunits by TNF α within the Context of Excitatory and Inhibitory Synapses of CA1 Pyramidal Neurons	79
Effect of TNF α on AMPARs	79
Effect of TNF α on GABA _A Rs	80
The Modulatory Effects of Neuroinflammation on Hippocampal Synaptic Plasticity. 81	
Pro- and Anti-inflammatory Actions of TNF α	82
TNF α Alters Hippocampal Synaptic Plasticity by Increasing the Frequencies and Amplitudes of Miniature Excitatory Postsynaptic Currents	83
Do The Excitatory Effects of TNF α Translate into Enhanced Hippocampal LTP?	84
Behavioral Studies of the Effects of TNF α on Hippocampal-Dependent Memory	84
Neuroinflammation Affects Vascular Units following TBI	85
Global Effects of rTBI: A Functional Shift Between Excitatory and Inhibitory Inputs to CA1 Pyramidal Neurons, The Potential Role of Dendritic Filtering.....	86
Hypothetical Model of the Impact of 3X CHI on Hippocampal CA1 Neurons	87

Volatile Anesthesia During Surgery: Possible Confounding Variable.....	89
Mitigating the Potential Impact of Isoflurane on Our Results.....	90
Detrimental Impact of rTBI on U.S. Military Servicemembers	91
Future Directions	93
Combining Optogenetics and Imaging Techniques to Reveal the Potential Clinical Relevance of This Thesis Project.....	94
Mindfulness-Based Cognitive Therapy / Acceptance and Commitment Training: Promoting Resilience in Neural Circuitry Prior to Trauma and Rewiring Damaged Networks Post-Trauma	96
Empirical Evidence of the Benefits of Mindfulness Training in Treating the Cognitive and Neurobehavioral Deficits Associated with rTBI.....	97
Mindfulness Training Results in Neuroanatomical and Structural Modifications to Regions of the Brain That Are Susceptible to Damage from rTBI.....	97
Mindfulness Meditation Triggers Epigenetic Changes in the Activity of Histone Deacetylases (HDACs) and in the Expression of Neuroinflammatory Genes	98
Effects of Mindfulness Training on Hippocampal Volume, Combat Resilience, and Symptom Severity of rTBI, PTSD, and Combat-related Sleep Disorders.....	99
Final Conclusions.....	100
REFERENCES	121

LIST OF TABLES

Table 1: Passive intrinsic membrane properties are unaffected by 3X CHI, one week after the final injury..... 110

Table 2: Four of the active intrinsic membrane properties are unaffected by 3X CHI, one week after the final injury. 111

LIST OF FIGURES

Figure 1: Model of repetitive TBI closed head injury.	102
Figure 2: 3X CHI impacted outcome of behavioral tests between 24 hours and one week following injury. (A).....	106
Figure 3: Schaffer collateral-CA1 synapses exhibit normal paired-pulse facilitation in 3X CHI mice one week after the final injury.....	107
Figure 4: Enhanced CA1 hippocampal long-term potentiation observed in 3X CHI mice one week after the final injury. (A).....	108
Figure 5: Active intrinsic properties of CA1 hippocampal pyramidal neurons are altered by 3X CHI one week after the final injury.	112
Figure 6: 3X CHI alters spontaneous excitatory postsynaptic currents (sEPSCs) of CA1 hippocampal pyramidal neurons one week after the final injury. (A)	113
Figure 7: 3X CHI alters miniature excitatory postsynaptic currents (mEPSCs) of CA1 hippocampal pyramidal neurons one week after the final injury.....	114
Figure 8: 3X CHI alters spontaneous inhibitory postsynaptic currents (sIPSCs) of CA1 hippocampal pyramidal neurons one week after the final injury.....	115
Figure 9: 3X CHI alters miniature inhibitory postsynaptic currents (mIPSCs) of CA1 hippocampal pyramidal neurons one week after the final injury.....	116
Figure 10: 3X CHI causes a shift between excitatory and inhibitory inputs to CA1 pyramidal neurons and changes to their intrinsic active properties.	117
Figure 11: Summary of electrophysiological changes in CA1 hippocampal pyramidal neurons resulting from 3X CHI.	118
Figure 12: Proposed mechanism for the neuroinflammatory-mediated differential subunit regulation of excitatory AMPA and inhibitory GABA _A receptors, and voltage dependent sodium and potassium currents that resulted from 3X CHI.	120

CHAPTER One: Introduction

MILD TRAUMATIC BRAIN INJURY: EPIDEMIOLOGY AND DIFFERENTIAL DIAGNOSIS

Traumatic brain injury (TBI) is the leading cause of death and disability worldwide for people under the age of 45 (158; 516). In the United States, over 1.7 million new cases of TBI are reported each year (158; 336; 516). Of the total cases of TBI, more than 80 percent are classified as mild TBI (mTBI) (96; 413). The very terminology used to define mTBI characterizes both the heterogeneity and complexity of this brain injury. mTBI, concussion, secondary impact syndrome, and even chronic postconcussion syndrome have been used interchangeably to describe mTBI (94; 96; 218; 228; 263; 291; 368; 377; 462). This absence of a clinically authenticated definition for mTBI has impeded the treatment of mTBI patients, and hindered the progress in research studies (94; 96; 228; 263; 368).

Twenty years ago a single mTBI was described as head trauma that presents with a loss of consciousness not to exceed 30 minutes in duration, transient amnesia of the injury and/or events prior to the head trauma, a Glasgow Coma Scale score between 13-15, and/or an altered mental state (e.g., reduced lucidity, confusion, disorientation) immediately following the traumatic event (288). The Department of Defense includes one more condition to this definition, and that is that diagnostic neuroimaging must be unremarkable and normal (106; 565). It is at this point that this terminology becomes ambiguous for clinicians. When these various signs/symptoms occur after the initial trauma, and continue to persist, it is unclear whether these impairments resulted from mild TBI or postconcussion syndrome (60; 106; 139; 230; 565). Clinical signs and symptoms consistent with mTBI and/or concussion typically subside within several

weeks after the primary impact (129; 377). However, if the neurological deficits continue after three months post-injury, the patient is then diagnosed with PCS (129; 253; 254; 296; 325; 342; 369; 377; 512).

The Diagnostic and Statistical Manual for Mental Disorders, fourth edition (DSM-IV), and the International Classification of Diseases, tenth edition (ICD-10) further contribute to the ambiguity between PCS and mild TBI, because their diagnostic criteria of mild TBI differ from that of the VA/DoD (60; 94; 565). Using these two clinical references may lead the physician to diagnose a mild TBI as PCS, because it is unclear if mTBI symptoms may simply be a case of PCS that was result from a mTBI (60; 94; 565). In civilian medicine, the ICD-10 is employed not only for the systematic classification of diseases, but it is now being used to drive the direction of research funding and to influence public health policy (420). At the time of writing this thesis, neither the Department of Veterans Affairs nor the Department of Defense accept the definition of PCS and diagnostic standards of neither the DSM-IV nor that of the ICD-10 (565). This lack of universally accepted diagnostic standards for mTBI creates difficulties for both the physician who uses them, as well as for the patient who encounters needless hindrances and bureaucratic obstacles during treatment and recovery from the injury.

For the clinician, these ambiguous diagnostic criteria for mild TBI address only the physiological disturbances of mTBI, while the symptoms, neurodegenerative time course, and degree of impairment are inadequately characterized (94; 228; 368). Likewise, these diverging definitions of mTBI present confounding variables for the basic science researcher. Variability of inclusion and exclusion standards for treatment

groups, unrepresentative samples, contradictory comparison groups, and inaccurate sample sizes all have contributed to the weakening of the experimental design and validity of the generated data (139; 230; 368; 381; 382; 415; 454). The consequences of the vague diagnostic definition of mTBI, combined with the difficulties it creates in interpreting data from mTBI research, have had a confirmed negative impact in cases of combat-related mTBI (228; 230). Collectively, these negative consequences may adversely affect the combat readiness of the troops. More than 300,000 U.S. combat veterans of the Iraq and Afghanistan wars have been diagnosed with a mTBI (228; 546). Treatment plans and therapeutic interventions to improve the neurocognitive outcome of these patients are impeded by the intense debate on mTBI diagnostic criteria and data interpretation of research studies (228; 230; 546). Specifically, patient noncompliance to a treatment plan increases when medications are prescribed for non-approved indications (228; 230). Furthermore, neurocognitive tests, whose resulting data is subject to varied interpretation, fail to address the comorbidity of mTBI with posttraumatic stress disorder (PTSD) (228; 230; 546). Clinicians devoted to the treatment and study of mTBI have proposed that separate categories must be established for cases of concussion, mTBI, postconcussion syndrome, secondary impact syndrome, and especially for the combat-relevant cases of repetitive traumatic brain injury (rTBI) (94; 101; 218; 228; 230; 462; 546). Based upon these recommendations from clinicians, this thesis focuses solely on rTBI, and its applicability to combat-related cases of rTBI and in athletes who play contact sports.

These multifaceted challenges in treating rTBI encompass clinical terminology, accurate diagnosis of the condition, efficacy of treatment plans, and ultimately the

reshaping of public policy for both civilian and military cases of rTBI. In order to achieve progress in all of these areas, an interdisciplinary approach is necessary to solve these problems created by rTBI. For the basic science researcher, a highly beneficial contribution one can make is to both reveal and clarify the underlying secondary mechanisms that drive the progression of neurocognitive deficits caused by rTBI. It is vital to characterize the pathophysiology initiated by the primary injury, because it can persist undetected for months to years until the patient manifests irreversible cognitive and behavioral deficits. No clinically authenticated and universally accepted definition of rTBI will ever be formulated, and improved care for the rTBI patient will not occur, without a more thorough understanding of the mechanistic pathways of the pathophysiology of rTBI.

REPETITIVE TRAUMATIC BRAIN INJURY (RTBI): PATHOPHYSIOLOGY

In cases of moderate-to-severe TBI, the pathophysiology of secondary injury is characterized by compromise of the blood brain barrier, trauma-induced activation of voltage-gated ion channels, glutamate excitotoxicity, calcium (Ca^{2+}) imbalance, mitochondrial dysfunction, necrosis, and apoptosis (98; 438). However, in the case of mild rTBI, this cascade of deleterious events does not occur with the intensity and duration as seen in moderate-to-severe TBI (28; 537). Rather, the aberrations in ionic currents, energy homeostasis, and cytoskeletal integrity caused by the primary injuries are both transient and rescindable (184; 210; 519; 537; 538). As these pathophysiological events dissipate and eventually are no longer detectable, the cognitive and behavioral deficits that resulted from the pathophysiology likewise become absent. In spite of improvement in majority of patients, 15 percent of patients with a previous diagnosis of

mTBI will continue to present with neurological deficits 12 months after the initial trauma (94; 210; 465; 537). However, the risk of the cumulative effect of rTBI on the long term neurological outcome of the patient should not be underestimated or ignored, as it is seen in the case of second-impact syndrome.

Second-Impact Syndrome: A Subcategory of rTBI Pathophysiology

Second-impact syndrome (SIS) results when a patient suffers an initial mTBI, and then experiences a second cranial impact before the symptoms associated with the initial mTBI have resolved and dissipated (87; 88; 107; 311; 329; 370; 377; 388; 404; 490). The second TBI is relatively mild, and it does not present with an immediate loss of consciousness (LOC) (377). However, in a period of minutes, diffuse cerebral edema, coupled with vascular engorgement, results in herniation of the brain, and the patient becomes comatose (263; 377). The proposed mechanism of deterioration is that the second mTBI may cause a sudden loss of cerebral blood flow (107; 163; 311; 377). The resulting compensatory release of catecholamines or other neurotransmitters triggers a sharp rise in intracranial blood volume, which produces the cerebral edema that ultimately leads to the comatose state (107; 163; 311; 377). The hallmark postmortem pathology of an SIS is a subdural hematoma, and all cases of SIS have been male athletes between the ages of 10-24, the majority (71 percent) of whom are high school football players (88; 107; 311; 377; 404). Although rare, second impact syndrome highlights the brain's vulnerability to excessive damage following mild rTBI.

Postconcussion Syndrome (PCS): Persisting Symptoms and Poor Outcome

The conflicting and/or overlapping terminology used to describe head injuries exacerbates the challenges in treating patients of head injuries. Thus, it is important to distinguish a mTBI/concussion from postconcussion syndrome (291). While mTBI and concussion are two clinically separate categories of head injury (211; 228; 230; 246; 291; 372; 383), neither fall into the classification of postconcussion syndrome (PCS). In the cases of concussion and mTBI, the initial clinical signs and symptoms that resulted from the head injury typically subside within several weeks after the primary impact (129; 377). However, if the neurological deficits continue after three months post-injury, the patient is then diagnosed with PCS (129; 253; 254; 296; 325; 342; 369; 377; 512). Even though cognitive deficits do present themselves with a diagnosis of PCS, the predominant signs and symptoms of PCS are behavioral and neuropsychological in nature (64; 129; 318; 368; 371; 372; 377; 512; 583). The severity of these behavioral deficits correlates with poor neurological outcome (64; 325; 512). PCS-associated behavioral deficits include major depression, anxiety, insomnia, irritability, emotional instability, and psychosomatic pain (372; 377). Maladaptive coping skills, such as catastrophizing, bitterness, anger, perceived injustice (i.e., victimhood), and high-risk behavior are also observed in PCS patients (325; 512). For many head injury patients, these manifestations of negative thinking and attitudes aggravate their depression and anxiety, delay their recovery, and contribute to poor outcome and prognosis (76; 143; 483; 512). If these cognitive and behavioral deficits continue for more than one year after the initial injury, then the patient is diagnosed with chronic postconcussion syndrome (CPCS) (263). Therefore, an animal model of repetitive injury should permit the investigator to monitor both the longitudinal alterations in microanatomy of neuronal

networks, and their function and impact on behavior long-term post-injury. Moreover, this optimized model or rTBI should also simultaneously preserve the physical integrity of the cranium with absence or minimal impact on skull fractures, post-injury apnea, and mortality.

Subconcussion: The Undetected Contributor of rTBI Progression and Pathology

Among all the TBI classifications, the phenomenon of subconcussion is the most difficult to detect in a living patient. In very general terms, a subconcussion is a TBI that does not produce the intensity of changes in acceleration/deceleration of a concussion, nor does it present with any obvious neurological deficits (205; 543). In some cases, however, sensitive neuropsychiatric examinations, functional MRI (fMRI) and diffusion tensor imaging (DTI) are able to detect clinical evidence of subconcussion (31; 144; 205; 543). The association between closed-head injury and subconcussion in contact sports is well documented (88; 89; 110; 114; 122; 182; 202; 218; 232; 240; 355; 372; 383; 410; 563). Biophysical analysis of the human brain demonstrates that it is the change in velocity, not the magnitude of velocity, that is the greatest risk factor in poor outcome from repeated subconcussive impacts (124; 517).

Cerebrospinal fluid (CSF) protects the brain within the cranial cavity by occupying the spaces between the brain and the cavity, and also by offsetting 95% of the weight of the brain (277; 396). Rather than being rigidly locked into place, the brain is suspended from the cranial cavity by the arachnoid trabeculae and CSF (277; 396). When subjected to linear, angular, and/or rotational forces, the brain will also accelerate/decelerate along with the surrounding CSF, and thus becomes at risk of impacting the interior of the cranial cavity (124; 517). The forces generated by the

primary impact cause this intra-cranial passage of the brain, which is termed “brain slosh” (124; 517). Subconcussive brain slosh has its most deleterious effect in the case of repetitive subconcussions, because their cumulative effect produces neurological damage that is practically undetectable with current diagnostic procedures (24; 517). CSF can also protect the brain by removal of neurotoxic compounds that may be produced and accumulated during and between injuries (599).

Despite the difficulty in detecting neurological deficits in patients that have sustained multiple subconcussions, recent studies are yielding novel tests to reveal subclinical changes in neurological performance. *The Repeatable Battery for the Assessment of Neuropsychological Status* is able to show that subconcussed athletes will present with memory impairments and lower total mini mental scores one week after injury (24; 292). fMRI can visualize the number of subconcussive impacts in relation to their anatomical distribution (24; 66). Bazarian et al. (31) employed diffusion tensor imaging to observe white matter damage in contact sport athletes who were asymptomatic for concussion or TBI (31). These athletes had a history of multiple subconcussive impacts and white matter lesions at a frequency three times higher than the subjects in the control group (24; 31). Based on numerous previous works, it appears that the mouse model of TBI can offer characteristics allowing it to be used as a preclinical model of mild repetitive injury, since the presence of human-like TBI pathologies of axonal and myelin abnormalities have been reported (478). Furthermore, it holds potential for use in imaging diagnostic methods such as diffusion tensor imaging in spite of poor spatial resolution (346). Also, the presence of CSF flow with its neuroprotective effects acts as a sink for potential neurotoxic molecules (249; 511).

CHRONIC TRAUMATIC ENCEPHALOPATHY: THE HALLMARK PATHOLOGY OF rTBI

Chronic traumatic encephalopathy (CTE) is the hallmark pathology of rTBI, and has been extensively investigated in postmortem studies on civilians and athletes who play contact sports (23; 30; 31; 102; 113; 127; 132; 133; 148; 263; 309; 310; 336; 360; 366; 367; 371-373; 376-378; 380; 428; 430; 449; 461; 462; 516; 533; 537; 561).

Investigators who pioneered CTE research in civilian populations are now conducting postmortem studies in military-related rTBI (98; 102; 133; 187; 289; 310; 379; 426; 429; 435; 533). With current typical diagnostic imaging methods and an absence of effective biomarkers, CTE can only be diagnosed *postmortem* (375-380). However, behavioral symptoms of the presence and progression of CTE can be clinically assessed by observing changes in personality, such as an increased incidence in high-risk behavior, impulsivity, aggression, depression, a loss of ambition or apathy, irritability, and suicidal ideations (376; 379; 380; 536). These progressive changes in mood and behavior are crucial clinical signs of CTE, because they tend to manifest themselves in the third, fourth, and fifth decades of life (376; 379; 380; 536).

Pathologically, CTE is categorized as a tauopathy, due to the expansive deposits of phosphorylated tau (PHF-tau) that accumulate histologically as neurofibrillary tangles (NFTs). A critical feature of CTE that differentiates it from other tauopathies is that it is perivascular, such that it collects within the depths of the cerebral cortical sulci (376; 379; 380; 536). This progressive spread of CTE histopathology is classified into four distinct stages (376; 379). Stage I is characterized by perivascular clusters of NFTs within the depths of the frontal, temporal, insular, or parietal sulci (375; 376; 379). In Stage II CTE NFTs are present in the cholinergic neurons of the nucleus basalis of Meynert and the noradrenergic neurons of the locus coeruleus, while the medial temporal

lobe remains absent of NFTs (375; 376; 379; 533; 536; 537). Stage III CTE consists of NFTs that have now spread throughout the medial temporal lobe, which includes the hippocampus, entorhinal cortex, amygdala and even the olfactory bulbs (375; 376; 379; 533; 536; 537). Stage IV CTE is the classification of the most severe cases of CTE where NFTs are pervasive throughout the entire brain, white matter demyelination is marked, and reactive microglia along with astrogliosis have invaded the subcortical white matter (375-380).

It is currently unknown how rTBI initiates the progressive neuropathology of CTE, but it is speculated that the hyperphosphorylation of PHF-tau, calpain-mediated cytoskeletal breakdown, axonal transport disruption, and the misfolding of tau all play key roles in the development of CTE (377; 379). Presently, postmortem analysis of the brains of 110 military veterans have resulted in the diagnosis of CTE in 23 cases (379). Among the confirmed cases of CTE, 4 of the cases are attributed to combat exposure to blast TBI, via improvised explosive devices (IEDs), while the other 19 cases are associated with contact sports, one assault, one motor vehicle accident, and one non-combat related concussion (379). The most important distinction between the combat cases of CTE versus the sports-related cases is that CTE symptomatic onset occurred in the combat cases between the ages of 20-49 (Stages I and II CTE), while the symptomatic onset of sports-related cases ranged from the ages of 50 or more (Stages II-IV CTE) (379). Regarding animal models of CTE, Petraglia et al., (447) have created a mouse model of the neurological behavioral deficits associated with CTE (447). However, there are currently no animal models that can reproduce the histopathological characteristics of CTE.

rTBI Patients That Present with Neurological Deficits with an Absence of Postmortem CTE Pathology

Despite the thorough and exhaustive evidence of the correlation between CTE pathology and rTBI-associated neurological deficits, there is a population of rTBI patients that exhibit neurological deficits consistent with rTBI, but have a total absence of hyperphosphorylated tau and NFTs (222). These deceased patients were retired professional football players who had sustained multiple concussions throughout the course of their careers (222), although CTE pathology is present in the overwhelmingly majority of rTBI patients whose brains were the subject of postmortem studies. The discovery of a population of rTBI patients free from CTE pathology however provides an important clinical rationale for conducting functional electrophysiological studies on rTBI. Because of its intrinsic sensitivity in the temporal domain, electrophysiological assessments of rTBI would likely identify patients who either display resilience against, or susceptibility to, the factors that accompany the initial stages of injury. Deleterious alterations in synaptic plasticity may occur years before the advent and spread of CTE pathology. Furthermore, a trauma-induced imbalance of excitatory-inhibitory synaptic inputs may very well precede *any* signs/symptoms of neurological and vascular damage (209). Just as Talavage et al., (543) demonstrated in their study tracking the neurological decline of teenage football players who were asymptomatic for rTBI and had unremarkable diagnostic neuroimaging (543), a rodent model of TBI could demonstrate electrophysiological and vascular changes in specific brain regions that occur very early within the therapeutic window. Identification of aberrant neuronal network activity could then be evaluated for its deleterious impact on neurocognitive behavior. Scientific

progress in this area would likely lead to novel efficacious therapies in the form of early and late stage pharmacological interventions.

THE RELATIONSHIP BETWEEN rTBI, CTE, AND POSTTRAUMATIC STRESS DISORDER (PTSD)

With the Iraq and Afghanistan wars has come the recognition of the comorbidity between rTBI and PTSD (229; 379). Currently rTBI, CTE, and PTSD are defined by psychiatric and behavioral dysfunction associated with damage to the frontal lobe, working memory, planning, multitasking, judgment, executive function, complex decision-making, sleep patterns, high-risk behavior, and impulsivity (153; 379; 533; 575). The symptoms overlap between these three clinically distinct neurological disorders, which complicates the clinical differential diagnosis. A structure / function relationship exists between the progressive clustering of NFTs and the degree of neurological deficits seen in the patient. As the accumulating PHF-tau progresses into the advanced stages of CTE (Stages III and IV), the severity of neurocognitive behavioral dysfunction increases. Currently, it is not known how CTE affects neural function and synaptic plasticity in living patients. Therefore, an examination of electrophysiological changes in animal models caused by rTBI may provide distinctions between rTBI and PTSD that could prove valuable to clinicians. A differential diagnosis exists between PTSD and rTBI, such that they have signs and symptoms that overlap between the disorder and the traumatic injury. Electrophysiological studies of rTBI may elucidate clear differences between PTSD and rTBI, and thereby will facilitate the clinical distinction between these two neurological disorders. In particular, animal models of combined PTSD and rTBI will have high likelihood of being instrumental for distinguishing differences between the neurological symptoms and the underlying longitudinal synergistic neuropathologies.

HUMAN ELECTROPHYSIOLOGICAL MANIFESTATIONS OF rTBI: THE P300 EVENT RELATED POTENTIAL

As it has been stated above, rTBI presents complex clinical challenges in both its detection with current neuroimaging methods and in its correct diagnosis, due to the absence of a clinically validated definition for rTBI. Quite recently, clinicians are able to use the electroencephalogram (EEG) as a potential diagnostic tool to recognize if a patient suffers from rTBI. It has been reported that changes in the EEG of an rTBI patient can be detected in the acute (initial hours to weeks), subacute (weeks to months) and chronic (more than 6 months) stages of the injury (213). These changes are exhibited in the event-related potentials (ERPs) that are recorded in an EEG. An ERP is measured from the scalp, typically from the parietal or occipital region, and is a series of positive and negative waveform deflections that correlate to a time-dependent stimulus or behavioral response (173; 213; 462). An ERP may therefore be useful in assessing neurological deficits in rTBI patients is the P300 ERP.

Sutton et al., ago (452; 541) were the first to describe the P300 ERP over 49 years ago , and it is defined by its amplitude range and latency (~ 300 ms duration) (452). An ERP amplitude is defined as the difference between the baseline prestimulus voltage level and the most positive deflection peak of the waveform, while the ERP magnitude reflects the patient's ability to focus attention (452). In other words, an increased latency would suggest that the patient is having difficulty processing information, while a decreased amplitude implies that the patient is unable to remain focused, and may have an attention deficit (190; 213; 450; 452).

Some clinical researchers employ the P300 ERP to evaluate cognitive deficits in single moderate-to-severe TBI (320), single mild TBI (16; 307), and rTBI (25; 72; 150;

173; 190; 397; 398; 551; 552; 593). Decreased amplitude and increased latency of the P300 ERP can correlate with deficits in learning and memory of elderly athletes that suffered their last mTBI in young adulthood (127). Moreover, pathological changes to the amplitude and latency of the P300 ERP can be detected even in patients who are asymptomatic and have unremarkable diagnostic structural neuroimaging (72). As seen in mTBI (127), numerous clinical studies of rTBI patients confirm that the general trends seen in the P300 ERP after rTBI are decreased amplitudes (25; 72; 73; 126; 190; 320; 397; 398; 551; 552; 593) and increased latencies (127; 173; 190; 320).

These human clinical electrophysiological results are highly relevant for our project for two primary reasons. First, the pathophysiological changes to the P300 ERP observed in rTBI patients serve as strong evidence that rTBI creates a shift between excitation and inhibition in human rTBI patients. Secondly, while the P300 ERP is recorded from the scalp, it is believed to be governed by our region of interest, the hippocampus (150; 172). While the P300 ERP is primarily a cortical event, the hippocampus not only contributes to its generation, but more specifically, it determines the latency of the P300 ERP (150; 172). Patients with impaired memory and that have lesioned hippocampi have increased P300 ERP latencies that are strongly correlated to the bilateral lesions (172). Moreover, atrophy of the hippocampus is also significantly correlated to increased latencies of the P300 ERP (150). These clinical findings serve as a basis for our rationale to select the hippocampus as our region of interest in the study of rTBI. It is intriguing to note that P300 ERPs were recently successfully used as the outcome measure in a rat model of vascular dementia with corresponding decreases in amplitude and increases in latency following injury (321).

A significant number of cognitive deficits related to rTBI are associated with hippocampal-dependent memory (23; 373; 375-380; 428; 430; 533; 536; 537).

Therefore, during the development of the model, we have evaluated hippocampal function using a battery of electrophysiological measurements in hippocampal slices. In fact, hippocampal slices have been used for over three decades to assess synaptic plasticity, and which relates plasticity to hippocampal function in multiple behavioral tests in the context of learning and memory assessments. (2; 57-59; 109; 169; 223; 277-279; 286; 305; 326; 327; 349; 350; 468; 524).

HIPPOCAMPAL-DEPENDENT MEMORY AND THE ROLE OF AREA CA1 IN LONG-TERM POTENTIATION

The hippocampus specializes in explicit (declarative) memory, which necessitates both attention and the deliberate effort to retrieve stored memories (277-279). Explicit memory is further categorized into semantic memory for academic facts, and episodic memory for people, places, and events (277; 278). Conscious attention is needed to first encode a new memory, and then later for the recall for the newly stored memory (279). Recent studies demonstrate that conscious attention discriminately fine tunes both the encoding and the recall of hippocampal-dependent memory by accentuating physiological reactions to task-related information (279; 411; 412). The term “experience-dependent plasticity” is often used to describe this process (278; 279), and the cellular mechanism employed by the hippocampus to successfully store and recall memories is frequently referred to as long-term potentiation (LTP) (277).

CA3-CA1 Schaffer collateral LTP fulfills the criteria of associative LTP first described by Hebb, because potentiation occurs only when a synapse is active while the postsynaptic cell is sufficiently depolarized, and any inactive (silent) synapses are not

potentiated unless LTP causes modification of synaptic AMPARs that, prior to LTP, were either not present in the postsynaptic membrane or were electrophysiologically silent (223; 251; 277-279; 365). Through this highly selective mechanism, the synapses become strengthened and actively participate in the electrical activity (e.g. firing) of the postsynaptic neuron (223; 277-279; 365). In this manner, an infinite combination of presynaptic neurons, each of which transmits unique information, can fire in a coordinated manner to form and strengthen new associations (memories) with the postsynaptic neuron (223; 277-279; 365).

In the area CA1, associative LTP requires the activation of the NMDA receptor (NMDARs) (277-279). To become activated, NMDARs need both the binding of glutamate (assuming that the glycine site is saturated) as well as sufficient depolarization to remove the Mg^{2+} block (277). Due to the reciprocal needs of both the NMDARs and the presynaptic neuron, NMDARs will become active only when sufficient depolarization occurs in a time-dependent manner that coincides with glutamate release from the presynaptic neuron (277-279). Once activated, the NMDARs permit the influx of Ca^{2+} into the postsynaptic neuron, which then contributes to the prerequisite depolarization for the induction of LTP to occur (277-279). This Ca^{2+} influx is responsible for initiating the various signaling pathways that are needed for the induction and maintenance of LTP (277-279). The complex interplay of signaling pathways involve the actions of calcium calmodulin kinase II (CaMKII), protein kinase C (PKC), protein kinase A (PKA), and mitogen-activated protein kinase (MAPK), promotes the insertion and activation of excitatory glutamatergic AMPA receptors (AMPARs) which after binding glutamate strengthen synapses between the presynaptic and postsynaptic neurons (277-279).

Through this tightly regulated and sequential process, the postsynaptic response is thereby augmented, and the ability to both store and recall new associative memories is now enhanced (277-279). This process and its relations to memory mechanisms are highly optimized, and either the decrease or enhancement of LTP are related to memory deficits (2; 62; 136; 174; 277-279; 402; 417; 418; 578).

VULNERABILITY OF THE HIPPOCAMPUS TO REPETITIVE TBI

The hippocampal head contains the majority of field CA1, which has been observed to be particularly sensitive to TBI (363). The anatomical relationships of the hippocampus render it susceptible to damage from TBI. In cases of TBI that are accompanied by increased intracranial pressure (ICP), the uncus of the temporal lobe can herniate through the tentorial notch of the tentorium cerebelli (396). The free edge of the tentorium cerebelli not only lacerates the uncus, but compresses the P2 segment of the posterior cerebral artery, causing both ischemia and sclerosis to occur in field CA1(151). Patients with atrophy of the left hippocampal head demonstrate verbal memory deficits (17). Clinicians have documented a high prevalence of injury to the medial temporal lobe with patients diagnosed with mTBI (564). Fifty percent of these patients reported deficits in semantic, episodic, and spatial memories, all of which are hippocampal-dependent in nature (472). Even in cases where neuroradiological lesions are absent, atrophy of the hippocampal head correlates with a negative cognitive outcome (434; 556). Post-mortem studies of retired professional football players who suffered multiple head injuries over the course of their careers exhibit both the gross and microscopic neuropathology of CTE in their hippocampi (23; 373; 375-378; 380; 428; 430; 533; 536; 537). The anti-PHF-tau antibody clone AT8 is an anti-paired helical fragment-tau

antibody clone that detects paired helical fragment-tau doubly phosphorylated at Ser202 and Thr205, serines 199 and 202, and serines 205 and 208 (455). Patients with CTE present with bilateral atrophy of the medial temporal lobes, and intense AT8 staining for hyperphosphorylated tau in field CA1 (23; 373; 375-378; 380; 428; 430; 533; 536; 537). Given the depth of this anatomical, histological, behavioral, and clinical evidence of hippocampal deficits following repetitive mTBI, it is necessary to better understand how plasticity mechanisms related to learning and memory, such as LTP, are affected by type of brain trauma.

ANIMAL MODELS OF REPETITIVE TBI

Over the past several years, a number of animal models have been developed to study the effects and mechanisms of mild TBI, with mice and rats as the animals of choice. Perhaps the most frequently used of these models is the closed-head injury (CHI) model in adult male C57Bl/6J mice, with the total impact number ranging from 2, 5, and upwards to 16 (41; 42; 248; 300; 313; 330; 332; 343; 407; 408; 506; 607). CHI differs from controlled cortical impact (CCI) in that there is no craniotomy performed. The injury is achieved by incising and retracting the scalp, and directly striking the cranium with an impactor tip ranging from 5-9 mm in diameter. The impact is confined to predetermined coordinates, and strikes this precise location at a specific angle, velocity, and dwell time. Immediately following the injury, the scalp is sutured and treated with an antibiotic ointment, and the mouse is placed in a warmed (35°C) cage to recover from anesthesia and the surgery (41; 42; 248; 300; 313; 330; 332; 343; 407; 408; 506; 607).

The CCI model utilizes the same type of impactor as the CHI model, but the impactor tip directly contacts the dura, which is exposed via the craniotomy (144; 243;

244; 447). Just as the CCI model employs mechanical energy to injure neural tissue exposed by the craniotomy, the weight drop injury model impacts the skull with no craniotomy performed (10; 171; 352; 353; 384; 391; 392). A weight of known mass is released from a precise height from the cranium (10; 171; 352; 353; 384; 391; 392). Many of these models have been recently reapplied to the study of repetitive mTBI, as discussed in the following sections.

The second most common injury model has been the repetitive blast model (86; 570-572; 586; 587). The injury was created by placing an adult rodent inside a blast shock tube, whereas the cranium is perpendicular to the blast wave (570-572; 586; 587). The blast model injury can be designed to permit free rotation of the head and neck, which provides an advantage in characterization of DAI resulting from the blast.

Histopathological Effects and Neurobehavioral Deficits of rTBI

In both rats and mice, each of the injury models has consistently demonstrated the association of the severity of neurodegeneration to the number of impacts, the time interval between impacts, and the degree of cognitive/behavioral deficits (41; 42; 86; 144; 171; 243; 244; 248; 280; 300; 313; 330; 332; 343; 352; 353; 383; 391; 392; 407; 408; 447; 459; 460; 473; 506; 570-572; 586; 587; 607). However, these studies do clearly affirm that repetitive injury correlates to poor outcome, to a greater degree than single mild TBI, and it is the time interval between impacts that governs the severity of deficits. Therefore, mechanistic studies of these models promise to provide important insights into the pathophysiology of TBI and to identify targets for potential therapeutic interventions.

Histopathological Effects of rTBI

Diffuse axonal injury (DAI) that results from rTBI (570; 572) is driven by an rapid upregulation of caspase-3 and calpain II (570), increased Fluoro-Jade B immunoreactivity, enhanced silver staining for neurodegeneration, and increased edema (587). Neuroimaging studies of rTBI report that DAI results in increased fractional anisotropy, and decreased radial diffusivity in rodents subjected to multiple impacts (86). The extent of microvascular and axonal damage is also associated with upregulated activity of superoxide dismutase (SOD) (391; 392). Moreover, this neurovascular damage is accompanied by increased activity of reactive microglia and heat shock protein 27 (Hsp27) (10). One study observed exacerbation of DAI 60 days post-injury (144).

The repetitive CHI mouse model has consistently demonstrated a correlation between increased microglia reactivity, tau histopathology, white matter damage, and the increasing severity of cognitive and neurobehavioral deficits (41; 42; 112; 248; 300; 313; 330; 332; 343; 407; 408; 425; 506; 607). While TBI rat models clearly offer the advantages of harvesting larger volumes of blood, CSF, and neural tissue, we selected the mouse for our rTBI model. This will permit us to investigate further more mechanistic hypothesis based on electrophysiological changes resulting from rTBI, including whole-genome transcript profiles, epigenetic mechanisms and use of variety of cell-specific transgenic/knockout strains, which are available via the Cre-lox recombination technology.

Cognitive and Behavioral Deficits Associated with rTBI

Rodents subjected to repetitive impacts demonstrated impaired performance on the rotarod test, where they had shorter latencies to fall and with no recovery 5 days post-injury (587). These behavioral deficits were correlated with increased Fluoro-Jade B

immunoreactivity, enhanced silver staining for neurodegeneration, and increased edema (587). Exposure to repetitive TBI causes DNA fragmentation in an neuroanatomically region-specific and time-dependent manner (586), and is significantly correlated to increased times in the righting reflex test (586). Furthermore, rodents subjected to multiple impacts demonstrated increased exploratory behavior, poor balance, and spatial memory deficits (280; 352; 353; 384). That is, by increasing the time between impacts, the rodents recover faster from the deficits caused by the preceding impact (280; 352; 384). These studies offer further evidence that a shorter inter-injury time interval is associated with poor cognitive and behavioral outcome (86; 352; 353; 384).

Hippocampal-dependent spatial memory and motor deficits are correlated to increased severity of DAI, cytoskeletal breakdown, and disruption of the BBB (313). Increased incidences of depression and impairments in social recognition have been observed in rodents exposed to repetitive TBI (300; 447). There is also a relationship between increased astrogliosis, DAI, and cognitive/behavioral deficits, such as those demonstrated in the novel object recognition (NOR) test (460).

Electrophysiological Studies of Single TBI in Hippocampus

To our knowledge, there has been only one published electrophysiological study of rTBI in rodents (20). Therefore, a review of electrophysiological changes associated with TBI will be restricted to single injury models (90; 134; 141; 146; 194; 196; 201; 241; 245; 247; 290; 315; 409; 419; 431; 432; 466-469; 479; 487; 497; 554; 555; 595; 612; 613). In contrast to the behavioral, neuroanatomical, and histopathological studies of rTBI, the overwhelming majority of single TBI electrophysiological studies have utilized the lateral fluid percussion injury (LFP) (90; 146; 194; 201; 241; 247; 419; 431;

432; 487; 497; 554; 555; 595; 612; 613). Moreover, the rat model has been favored in electrophysiological single TBI studies over the mouse model (90; 134; 141; 146; 196; 201; 241; 247; 290; 315; 409; 419; 431; 432; 466-469; 487; 554; 555).

Single TBI Studies That Demonstrate Increased Hippocampal Excitability

Transient hyperexcitability exclusively in CA1 pyramidal neurons was observed in that both spontaneous and induced action potentials in CA1 neurons had increased frequencies at 2 hours and 24 hours post-injury, but the heightened excitability was no longer detectable 3 days post-injury (196). Whole-cell patch-clamp recordings of dentate granule cells (DGCs) 8-13 weeks post-injury revealed reduced inhibitory input to these neurons, because the frequencies for both sIPSCs and mIPSCs were decreased, but with no significant change in paired-pulse ratio (245). Increased excitability in injured CA1 neurons has been observed 7-9 days post-injury (90; 431; 432). These CA1 neurons ipsilateral to the injury demonstrated increased slope of the I/O curves and also frequencies of the mEPSPs (90). This enhanced CA1 excitability one week post-injury was attenuated by the administration of diazepam or the inducing a slightly hypothermic state (90; 431; 432). Increased excitability has also been reported in whole-cell recordings of DGCs from one week and up to one month post-injury (487). Whole-cell recordings of semilunar granule cells (SGCs) in the molecular layer of the dentate gyrus also exhibit increased excitability one week post-injury (201). The patch-clamped SCGs ipsilateral to the injury displayed a significant decrease in GABAergic tonic inhibitory currents, while the granule cells demonstrated increased tonic inhibitory currents, although no LTP measurements had been performed (201).

Single TBI Studies That Demonstrate Decreased Hippocampal Excitability

In contrast to the studies mentioned above, extracellular recordings of hippocampal slices ipsilateral to the injury have demonstrated a pattern of reduced excitability, as seen in the inability to evoke LTP as well as a decreased population spike threshold (468). These transient impairments were observed between 3 hours and 2 days post-injury, with the neurons recovering by day 7 post-injury (466-469). Another study in which extracellular recordings were conducted 7 days post-injury demonstrated impaired excitability in field CA1, which was exemplified in depressed I/O curves and the inability to evoke LTP (612; 613). A longitudinal study reported that Schaffer collateral LTP was significantly decreased at 2 weeks post-injury, but recovery from these deficits was observed with the administration of the selective phosphodiesterase inhibitor rolipram (554; 555). Whole-cell patch-clamp recordings one week post-injury have demonstrated decreased mEPSC amplitudes, with a corresponding increase in mIPSC amplitudes in mossy hilar cells (241). Extracellular recordings conducted 7 days post-TBI of CA1 neurons ipsilateral to the injury exhibited a failure to evoke LTP, but were successful in inducing LTD (497). Furthermore, the NMDAR-mediated potentials were reduced in the CA1 neurons from injured mice (497). In another study, whole-cell recordings of CA1 neurons ipsilateral to the injury revealed increases in the mIPSC amplitude and charge transfer, while recordings of DGCs exhibited decreases in frequency and amplitude for both sIPSCs and mIPSCs (595). This dysfunction of the inhibitory circuitry in the hippocampus contributes to the imbalance between excitation and inhibition caused by TBI (595). In summary, the imbalance between excitation and inhibition caused by TBI may result in either enhanced or diminished excitability. Experimental variables that may determine observed electrophysiological changes

include, injury model, impact coordinates, anatomical location of recording, rodent strain, rodent sex, and time of recording.

RATIONALE AND HYPOTHESIS

rTBI initiates a heterogeneous and complex array of cellular responses in the brain that contribute to acquired post-injury neurodegenerative and behavioral disorders. When exposed to multiple TBIs, the severity of damage and corresponding behavioral changes are often significantly worsened longitudinally. Animal models of rTBI have characterized the cognitive and behavioral decline associated with the cumulative damage caused by rTBI (10; 41; 42; 86; 112; 144; 193; 243; 244; 248; 280; 300; 313; 330; 331; 343; 353; 384; 391; 392; 407; 408; 425; 447; 448; 459; 460; 506; 570-572; 586; 587; 607). However, the cellular mechanisms underlying these changes have not yet been elucidated, which impedes the development of effective therapeutic approaches. We suspect that this deteriorating outcome is paralleled by degeneration of the mechanisms underlying activation and regulation of CNS neuronal network plasticity.

As was discussed in the previous pages, single TBI hippocampal electrophysiological studies have reported increases in both excitatory and inhibitory drives post-injury. However, the majority of the single mild TBI studies observed decreased hippocampal excitability and/or increased inhibition (241; 466-469; 497; 554; 555; 595; 612; 613). Therefore, it would be a reasonable assumption that multiple impacts delivered within a specific time interval would result in synergistic or additive attenuation of neuronal excitability in CA1 neurons ipsilateral to the injury. This impaired excitability would be manifested and clearly observed in both extracellular field potential and whole-cell patch-clamp electrophysiological recordings. Within this

context provided by the rationale, we hypothesized that mild repetitive TBI will result in either the failure to induce LTP, or a significant reduction in LTP when compared to the sham-injured group. This absent or reduced LTP will be accompanied by alterations in the properties of CA1 pyramidal neurons consistent with its slower intrinsic electrical activity. Furthermore, the excitatory postsynaptic currents, action potential-dependent and independent, will be decreased, whereas inhibitory postsynaptic currents, action potential-dependent and independent, will be increased in the triple injury group. In order to test our hypothesis, we proposed the following Specific Aims:

Specific Aim 1: To identify changes in CA1 hippocampal long-term synaptic potentiation (LTP) following repetitive mild TBI.

Specific Aim 2: To determine changes in the intrinsic electrophysiological properties of CA1 neurons, and to detect any shift(s) between excitatory and inhibitory CA1 networks.

This thesis is an initial step toward the long-term goal of better understanding the mechanisms of repetitive brain injuries that deleteriously affect synaptic plasticity, and therefore learning and memory processes in a model that simulates clinical cases of rTBI where the patient sustains additional TBIs while not yet having fully recovered from the previous impacts. This could contribute to the design of rational behavioral therapies and environmental enrichment paradigms based on targeted reactivation of network plasticity and recovery of balance between excitation and inhibition. In summary, the data generated by this project should help to unravel therapies that would inhibit rearrangements in hippocampal channel and receptors and provide novel targets to monitor devastating consequences of repetitive mild TBI in its initial course.

CHAPTER Two: Triple Closed-Head Injury (3X CHI) Model of Repetitive TBI (rTBI)

KEY ELEMENTS OF THE EXPERIMENTAL DESIGN OF rTBI

When creating and validating an animal model of rTBI, the following characteristics of rTBI are integral to the experimental design. The cumulative effect of the repetitive impacts has a greater influence on poor outcome than the magnitude of the blunt force trauma (14; 306; 380; 461; 537; 592). For each individual impact, it is not the force per se, but the sudden change in acceleration/deceleration that transfers stress and strain on the brain (24). Another critical factor in rTBI is the time interval between the initial and the successive impacts (392). This time interval of vulnerability has the potential of becoming a confounding variable, because it differs not only between humans and animals, but also between different types of animal models of rTBI (331; 392; 459; 548; 567-569). Recent publications have demonstrated that when the temporal window of vulnerability is modeled accurately for rTBI, it is possible to observe some injury-related microvascular damage, diffuse axonal injury, cognitive/behavioral dysfunction, and changes in electrophysiology within the region of potential. impact (20; 171; 244; 313; 391; 392; 460; 463; 506).

RATIONALE FOR USING CLOSED-HEAD INJURY TO MODEL rTBI

As it was elaborated in the Introduction, contact sport athletes and Servicemembers who have served on multiple combat deployments are susceptible to sustaining rTBI (187; 336). The military relevance for the closed-head injury model has been documented in recent studies. Upwards to 35% of all veterans of the Iraq and Afghanistan wars suffer at least one mild TBI, which translates into over 320,000 cases

of combat mTBI, and due to multiple deployments likely led to rTBI (343; 471; 546). Over 85% of all combat-related rTBI is closed-head injury in nature (280). In both animals and humans, repeated non-penetrating CHIs evoke likely cumulative pathophysiological alterations and behavioral deficits (67; 68; 104; 105; 507; 570). Moreover, the closed-head injury model offers several advantages over other models when studying rTBI. The CHI model produces the characteristic pathology of rTBI (108), demonstrates high reproducibility (407), and minimizes the incidence of skull fractures, and excessively high numbers of animals per treatment group (7; 71). Moreover, because no craniotomy is involved in the CHI model, the procedure does not trigger overstimulation of the proinflammatory cascade that is typically associated with the fluid percussion injury and controlled cortical impact craniotomy models (108; 407). The mouse was chosen over the rat animal model, because mice have well characterized genome and transcriptome, which would constitute an excellent base for future epigenetic studies to follow our functional electrophysiological approach (587). Moreover, the existing mouse repository offers access to a diverse variety of transgenic and knockout mice in specific neuronal populations (587).

METHOD FOR CLOSED-HEAD INJURY SURGERY

The closed-head injury (CHI) was created by employing an electromagnetic controlled cortical impact device (Leica Impact One™ Stereotaxic CCI Instrument, Buffalo Grove, IL), which provides high reproducibility of closed-head injury. The repetitive CHIs are performed as follows. Each surgery was performed at the same time of the day, with one CHI administered every 24 hours for 3 consecutive days. Under a 2% isoflurane/oxygen mixture of anesthesia, a rostral to caudal incision is made to retract

the scalp. The impact coordinates from the bregma are (in mm): X (lateral): 3.0, Y (posterior): -2.0, Z (ventral): -1.5. The angle of the 5 mm diameter impactor tip is set at 15° so that the impactor tip is approximately perpendicular to the surface of the skull. The CHI is delivered with a velocity of 4 m/sec, and a dwell time of 100 ms. These coordinates and impact parameters define the neocortical peri-infarct site (Figure 1). After each surgery, the scalp is closed with sutures and mouse is kept on the heated pad (36°C) during anesthesia. The mice are returned to the clean home cage (maximum of four mice per cage) with food and water *ad libitum*, and the cage is kept on a heated pad (38°C). After each injury mouse is closely observed for ~1-2 hours by the investigator to detect any abnormal behavior. The cage is then moved to the regular animal room, where the animals are monitored by laboratory and veterinary staff for any abnormal status. The Sham mice underwent all handling like the CHI mice, with anesthesia, opening of the scalp, and suturing of the skin, except the impactor tip was not released. Three repetitive injuries and/or sham surgeries were performed for three consecutive days approximately at the same time of the day.

EXPERIMENTAL DESIGN OF OVERALL RTBIs STUDY

As described above, our laboratory developed a mild repetitive closed-head injury model of TBI in mice to produce a stereotaxically reproducible mild closed-head injury (71; 170; 313; 323; 332; 480; 566).

The overall study design included experiments with groups of male C57Bl/6 (NCI, Poolesville/Frederick, MD) mice, 6-7 weeks old at the time of delivery (to model the age of young soldiers) subjected to single (1X CHI) and triple (3X CHI) closed-head injuries, along with their respective sham controls (1X Sham and 3X Sham) injured mice.

For the behavioral and molecular analysis study, a naïve group was included (no surgery and anesthesia were performed), and all the C57Bl/6 mice (male and 6-7 week old as well) for these studies were ordered from Taconic Company, Germantown, NY. Independently of the source all mice after delivery were acclimated for one week, and were kept on reversed light cycle in regular animal rooms throughout the surgeries and behavioral testing until the time of sacrifice for molecular characterization and/or electrophysiological experiments.

In characterizing this model we found that 3X CHI and 1X CHI mice may have some minimal skull fracture (only during the final, third impact), with no visible hemorrhaging. There were detectable histopathological changes in the brain within the first 3-4 days after the final injury, as it was assessed by Dr. Eric Lombardini, Veterinarian-Pathologist, U.S. Army, LTC, AFRI/USUHS). However, a loss of dentate gyrus (DG) granule neurons (>20% deficit, stereologically counted) in the 3X CHI ipsilateral hippocampus was noted even at 24 hours (after the third and final injury) throughout the 1-2 week period (data not shown, Dr. Ranjana Verma, Dr. Galdzicki's laboratory).

In collaboration with the Dr. Neil Grunberg laboratory, a series of behavioral assessments of 1X CHI, 3X CHI, 1X Sham, 3X Sham, and naïve mice were carried out. We selected the mouse neurological severity scale-revised scores (mNSS-R), rotarod test, and the open field (OF) behavioral paradigm. The goal of the mNSS-R is to assess motor and sensory reflexes (balance, landing response, ear reflex, eye reflex, sound reflex, tail pinch, and foot pinch; Figure 2A). The observer was blind to the origin of the experimental group, and scored the performance of the mouse using values ranging from

0 to 2 (Figure 2A). Mice used in the behavioral experiments were divided into 6 groups (1X TBI, 1X Sham, 3X TBI, 3X Sham, and respective naïve groups). For mNSS-R testing, the mice were assessed 24 hours after injury, and also two weeks post-closed-head injury (1X CHI and 3X CHI). At the 24 hour time point following CHI, the mNSS-R scores were elevated > 2-fold and ~ 3-fold for the 1X CHI and 3X CHI groups, respectively (Figure 2A). Two weeks after CHI, the scores of the CHI mice were not statistically different from the control mice, although the scores for the 3X CHI mice displayed a trend towards elevation. Interestingly, the rotarod performances, which provides information about balance and motor coordination, where the shorter time indicates compromised motor performance, was only significantly impaired at 24 hours for the 3X CHI mice (Figure 2B). In the OF tests, horizontal activity (HA) was assessed, which provides general information about movement and health. Moreover, vertical activity (VA), which correlates to escape and exploration, and is inversely related to “depression”, was also assessed in the OF tests. Lastly, the OF tests provides information about anxiety-related behavior, where greater scores indicate less anxiety, by assessing the center time with the ratio of center time/movement time (CT and CT/MT).

The most consistent and dramatic finding of the OF behavioral analysis was dramatic reduction in VA for the 3X CHI mice (> 4-fold) and the 1X CHI mice (~ 2-fold) at the 24 hour time point, whereas at the 2-week time point the vertical activity was unexpectedly increased (Figure 2C). These behavioral results carried out by the Grunberg laboratory suggested that following injury there is an active process of restoration of certain behavioral phenotypes. However, these results still suggest that this

behavioral impairment indicated that the deleterious 3X CHI impact still persists within the neurological domain at the one-week time point.

There is a spectrum of neurological impairments seen in other mouse models of TBI where behavioral and neurophysiological abnormalities have been reported (123; 497; 589; 617). As we mentioned above, the hippocampal-mediated impairments have a prominent signature in the course of TBI. Therefore, we assessed the hippocampal function using trace-cued and contextual fear conditioning tasks on the third post-TBI day. The results were consistent with a significant impairment in context-dependent tests, implicating the 3X CHI impact on hippocampal function (data not shown Verma et al., unpublished). These findings, and their possible correlation with microglial activation, and the indication of the microglia autophagy, will be pursued in future studies.

The results of the fear-conditioning tests strongly suggest that hippocampal synaptic plasticity, as well as hippocampal neuronal activity, are likely impaired in these mice. In order to determine the synaptic plasticity mechanisms that are impaired in mice subjected to 1X CHI and 3X CHI, we performed field electrophysiological recordings and induced LTP using high frequency tetanus in hippocampal slices isolated from injured mice one week after the final injury. In the first step, we determined the impact of injury on LTP that was induced in the CA1 region in slices isolated from 3X CHI mice, and compared them to LTP induced in mice subjected to 1X CHI and to sham-control mice.

CHAPTER Three: Extracellular Field Potential Recordings (LTP/PPF)

RATIONALE

In order to gain insight into the pathophysiological mechanisms underlying rTBI-induced hippocampal and behavioral impairments we performed an assessment of neuroplasticity mechanisms using standard electrophysiological tools. We selected the one-week time point after injury, since the mNSS-r score was still significantly elevated at this time point. In order to evaluate synaptic changes we employed the extracellular – field recording technique, which measured the summed response from a population of CA1 neurons that reside within the vicinity of the recording pipet.

METHODS FOR ASSESSMENT OF PAIRED-PULSE FACILITATION (PPF) OF SCHAFER COLLATERAL-CA1 SYNAPSES AND LONG-TERM POTENTIATION (LTP) EXPERIMENTS IN THE CA1 AREA OF THE HIPPOCAMPUS

The extracellular field potential recordings that were conducted to evoke LTP and paired-pulse facilitation (PPF) were modeled after Siarey et al., (509), with the exception that 400 μ m parasagittal hippocampal slices were used. Parasagittal slices were chosen based on the results obtained by Kriz et al., and Pastoll et al., (304; 440). The parasagittal orientation of the hippocampus optimizes the integrity of the Schaffer collateral axons, which project from the CA3 pyramidal neurons, and synapse on the CA1 postsynaptic dendritic spines (277; 304). Furthermore, parasagittal slicing protocols have been successfully used on adult mice that are up to 1.5 years in age (440). One of the key advantages of parasagittal slices is that they are cut by a Leica VT1200S vibrating blade microtome (Buffalo Grove, IL, USA). The manually-operated McIlwain tissue chopper (Brinkmann, Westbury, NY, USA) creates confounding variables, because it is subject to

high variability of the thickness and integrity of the hippocampal slices. However, the fully automated Leica VT1200S generates high quality parasagittal hippocampal slices with a consistently reproducible thickness of 400 μm . This optimization of hippocampal circuitry and viability of the slices allows us to record in excess of 8 hours after sacrificing the mouse (577). The detailed protocol for slice dissection is described below.

For the extracellular field potential recordings, the mice were anesthetized with isoflurane, immediately decapitated, and the brain was rapidly removed and placed in ice-cold cutting solution that contained (in mM): NaCl 119, NaHCO_3 26.2, D-Glucose 11, $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 9, NaH_2PO_4 1, KCl 2.5, CaCl_2 2.5 and bubbled with a mixture of 95% O_2 / 5% CO_2 (509). Parasagittal slices, 400 μm thick, were rapidly transferred to a holding chamber at the interface between warm (34°C) standard ACSF (pH 7.4) that contained (in mM): NaCl 119, KCl 2.5, NaH_2PO_4 1, D-Glucose 11, NaHCO_3 26.2, $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 1.3, CaCl_2 2.5 and bubbled with a mixture of 95% O_2 / 5% CO_2 (509). For recordings, parasagittal hippocampal slices were transferred to the recording chamber at the interface between warm (32°C) standard ACSF and humidified gas (95% O_2 / 5% CO_2). The slices were superfused (1 ml/min) and allowed to equilibrate in the recording chamber for at least one hour prior to recording (509).

The field excitatory postsynaptic potential (fEPSP) was recorded using an Axon amplifier and patch pipette backfilled with standard ACSF. The electrode configuration for our field potential recordings is as follows. A concentric bipolar platinum stimulating electrode was inserted in area CA3, and the recording glass borosilicate pipette, filled with standard ACSF, was placed in the stratum radiatum.

In order to assess paired-pulse facilitation (PPF) of Schaffer collateral-CA1 synapses a constant stimulus intensity (mA) that evokes 30% of the maximal field excitatory postsynaptic potential (fEPSP) response was used, and a 30-minute stable baseline was acquired. Immediately after achieving the baseline, the PPF protocol was started. The sweep time was set to 600 ms. Five consecutive waveforms were averaged into a single waveform, and their initial slopes (mV/ms) were also averaged into a single value as well.

For each pulse interval, a single value was acquired by averaging five consecutive waveforms that were obtained by applying a single stimulus of constant intensity of 1-5 mA every 60 s. The pulse intervals (ms) used were: 500, 400, 300, 200, 100, 80, 50, 40, 30, 20, 10. The expected general trend with this protocol was to see an increase in percent slope change (mV/ms) with the second stimulus, when compared to the initial slope of the first stimulus. Facilitation is generally observed beginning at a pulse interval of 200 ms, continuing through the 80 ms pulse interval, and then a depression observed from the pulse intervals of 50 ms to 10 ms.

To assess for associative CA1 hippocampal LTP fEPSPs were evoked from the Schaffer-collateral commissural pathway for associative LTP, and the fEPSPs were adjusted to 30% of their maximal response (509). The fEPSPs were digitized using a Universal Imaging PC and WinLTP version 2.30D LTP-acquisition software (Dr. William Anderson, Department of Anatomy, University of Bristol, UK; (13; 509)). A baseline was achieved by applying a single stimulus every 60 seconds for 30 minutes. The stimulus intensity (mA) remained constant, and was the same intensity that evokes 30% of the maximal fEPSP response. CA1 LTP was induced with a single train 100 Hz

for 1 s high frequency stimulation (HFS) (508; 509). The post-tetanic stimulation phase of the recording averaged five consecutive waveforms and their individual initial slopes (508; 509). Repeated-measures ANOVA statistical analysis was used to compare the differences in percent slope change (mV/ms) between the CHI and sham-injured mice. Values are given as means $\pm$ SEM, and the statistical significance was taken as $p < 0.05$ (508; 509).

RESULTS OF PAIRED-PULSE FACILITATION OF SCHAFER COLLATERALS SYNAPSES

Referring to Figure 3, while paired-pulse facilitation (PPF) was observed in all three treatment groups, there was no significant difference between the 3X CHI ipsilateral group and the 3X CHI contralateral, and the 3X Sham-injured group. In all three treatment groups, facilitation began at the 300 ms stimulus interval, and persisted until approximately the 80 ms stimulus interval. At the 50, 40, 30, 20, and 10 ms stimulus intervals, a depression was actually observed. Statistical analysis was performed by using repeated measures ANOVA ($p < 0.05$). PPF was observed in all treatment groups, and the percent slope change was not statistically significant when compared between treatment groups. There are other mouse models of neurodegeneration that display abnormal CA1 synaptic plasticity with an otherwise normal presynaptic activity seen in PPF recordings. In the mouse model for Down syndrome, Ts65Dn, Siarey et al., (510) documented pathophysiological changes in CA1 plasticity, while observing that the percent slope change in PPF recordings were statistically insignificant with control mice (510). Accordingly, we also conclude that the PPF recordings demonstrate that presynaptic activity in Schaffer collateral afferents in triple-injured ipsilateral hippocampal slices was unchanged.

RESULTS OF LONG-TERM POTENTIATION IN THE AREA CA1 OF HIPPOCAMPUS

For the 1X CHI ipsilateral treatment group, 16 ipsilateral hippocampal slices were used from 14 mice. For the 1X Sham- treatment group, 9 slices were used from 9 mice. Consistent with result of fear-conditioning experiments (data not shown), LTP measurements from single injured 1X CHI mice yielded no significant differences between treatment groups (Figure 4A). For the 3X CHI ipsilateral treatment group, 21 ipsilateral hippocampal slices were used from 13 mice. For the 3X CHI contralateral treatment group, 22 contralateral slices were used from 12 mice. For the 3X Sham-combined treatment group, 30 slices were used from 17 mice. Unexpectedly and opposite to what we hypothesized, the triple-injured ipsilateral slices displayed enhanced LTP, when compared to the triple-injured contralateral and sham-injured slices. Referring to Figure 4B, significantly enhanced LTP was observed in the 3X CHI hippocampal slices that were ipsilateral to the injury, with respect to the 3X CHI contralateral and 3X Sham-injured slices. While LTP was achieved in all treatment groups, the magnitude of potentiation was greater in the 3X CHI ipsilateral slices, than that observed in the 3X CHI contralateral and 3X Sham-injured slices. Statistical analysis was performed by using repeated measures ANOVA ($p < 0.05$).

In summary, these data generated from the extracellular field potential recordings demonstrate significant enhancement of synaptic plasticity of Schaffer collateral afferents on CA1 pyramidal neurons, and therefore suggest changes in the level of excitability and/or a shift in excitatory and inhibitory drives. However, the field potential experiments cannot detect changes in electrophysiological properties, and excitatory and inhibitory drive on a single-cell level. In order to identify these alterations at the level of the single pyramidal neuron, the whole-cell patch-clamp recordings will be discussed in

the subsequent chapters to address the impact of rTBI on electrophysiological intrinsic properties, and then on the excitatory and inhibitory synaptic activity observed in individual neurons from area CA1 with a purpose to identify possible causes that may lead to better understanding of the impact of rTBI on augmentation in LTP and hippocampal circuitry.

CHAPTER Four: The Impact of rTBI on Intrinsic Membrane Properties in CA1 Pyramidal Neurons

RATIONALE

The outcome of the evaluation of synaptic plasticity indicates that only the 3X CHI trigger alterations in LTP. The results also suggest that presynaptic elements in Schaffer collateral afferents are not affected by the injury. Therefore in subsequent experiments, we followed up on these LTP experiments with patch-clamp recordings from pyramidal neurons in ipsilateral hippocampal slices from 3X TBI and 3X Sham-injured mice. Our goal was to obtain new information about CA1 functional circuitry, and possibly relate it to changes in LTP and therefore hippocampal function. In addition, we planned to obtain a new insight into impact of repetitive injury on properties of CA1 pyramidal neurons and their interactions with excitatory and inhibitory networks.

SLICE PREPARATION

3X CHI or 3X Sham-injured male mice, 7-8 weeks old, were anesthetized with isoflurane, decapitated, and the brain was rapidly removed and placed in ice cold ($\sim 4^{\circ}\text{C}$) high-sucrose ACSF cutting solution containing (in mM): sucrose, 206; NaHCO_3 , 26; D-glucose, 10; MgSO_4 , 2; $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, 1; NaH_2PO_4 , 1.25; KCl, 2; CaCl_2 , 1, bubbled with a mixture of 95% O_2 / 5% CO_2 . Parasagittal slices, 400 μm thick, were cut with a Leica VT1200S vibrating blade microtome (Buffalo Grove, IL, USA), and immediately transferred to a warmed ($\sim 34^{\circ}\text{C}$) solution of whole-cell recording ACSF containing (in mM): NaCl, 126; sucrose, 20; NaHCO_3 , 26; D-glucose, 10; KCl, 3; NaH_2PO_4 , 1.25; MgSO_4 , 2; CaCl_2 , 2, bubbled with a mixture of 95% O_2 / 5% CO_2 . After 30 minutes, the

slices were transferred to room temperature ($\sim 21^{\circ}\text{C}$), where they were maintained for at least 1 hour before recording, while continuously being bubbled with 95% O_2 / 5% CO_2 .

ELECTROPHYSIOLOGY

Whole-cell patch-clamp recordings of cells located in area CA1 were performed seven days after the final CHI or sham injury. Using a Hamamatsu C2400 CCD IR camera, cells located in area CA1 were identified, and a whole-cell patch-clamp configuration was obtained with a borosilicate patch pipette of resistance 3-5 $\text{M}\Omega$ containing (in mM): potassium-gluconate, 130; NaCl, 15; EGTA, 1; HEPES, 5; Mg^{2+} -ATP, 4; Na^{+} -GTP, 0.3; CaCl_2 , 0.2. The pH was adjusted to 7.3 with KOH, and the osmolarity was calculated at 285 mOsm. A 5mV hyperpolarizing step from a holding potential of -70 mV was applied to estimate the membrane capacitance (C_m) and membrane resistance (R_m) at the initiation of the whole-cell access and at intervals throughout the recording. Likewise, the resting membrane potential (V_m) was measured in current-clamp (zero current mode) at the beginning of each recording, and monitored throughout the experiment to assess and monitor cell viability. Recordings were performed in voltage-clamp configuration and data acquired with an Axopatch 200B amplifier (Axon Instruments / Molecular Devices, Sunnyvale, CA), filtered at 10 kHz (Lowpass Bessel filter at 80dB/decade, NPI, ALA Scientific Instruments, Inc., Westbury, NY, USA). Data was acquired and stored on a Dell Optiplex 780 personal computer using Clampex acquisition software (Axon Instruments).

Action potentials were elicited from regular-spiking neurons in area CA1 at increasing steps (20 pA) while recording in I-Clamp Normal mode at -70 mV with pClamp analytical software. Spike threshold was evaluated by visually identifying the

voltage at which maximum acceleration occurred within the rising phase of the first spike of the neuron. We generally observed that the first action potential in these neurons exhibited multiple spikes (ranging from 2-10 spikes). The IGOR analysis program, written in house by Dr. Nathan P. Cramer, was written to analyze only the first spike. The IGOR analysis program measured the spike amplitude (pA), half-width at half-amplitude (ms), threshold (mV), rheobase (pA), average firing frequency (Hz), antipeak amplitude (mV), maximum rise slope (mV/ms), and maximum decay slope (mV/ms).

RESULTS OF INTRINSIC MEMBRANE PROPERTIES EXPERIMENTS

Referring to Table 1, 3X TBI had no significant effect on the passive intrinsic membrane properties, one week after the third and final injury. Resting membrane potential, membrane capacitance, membrane resistance, and the membrane time constant τ were all statistically unchanged. However, for four of the eight active intrinsic membrane properties, a significant difference was seen in the 3X TBI treatment group (Table 2 and Figure 5). Referring to Figure 5, the triple-injured mice displayed a larger action potential amplitude, a decreased half-width at half-amplitude, and increased maximum rise slope, and an increased maximum decay slope. Statistical analysis was performed using a Student's t-test ($p < 0.05$).

The absence of changes in the passive properties suggests that while 3X TBI alters the network activity (i.e., enhanced LTP), the electrophysiological properties of the individual CA1 neurons, such as size (capacitance), membrane resistance, and membrane resting potential were unaffected by the triple injury. However, the significant differences of the active membrane properties serve as evidence that the triple-injured CA1 neurons exhibit changes in somatic and perisomatic voltage-dependent channels that

make APs slightly larger and narrower in these neurons in comparison to APs recorded from sham-injured mice. The increases in voltage-dependent sodium and potassium currents, reflected in the maximum rise and decay slopes, suggest that the balance between these currents was altered in the triple-injured mice. Interestingly, no other changes in frequency of fringing of APs and their threshold to evoke AP have been detected following rTBI.

CHAPTER Five: rTBI Affects the Network Properties in Area CA1 of the Hippocampus

RATIONALE

The results presented in Chapter 4 showed normal intrinsic passive properties, but alterations to AP characteristics consistent with modifications to the excitable properties of CA1 neurons. In order to unravel the functional network properties of these neurons in subsequent experiments, we evaluated AP-dependent excitatory postsynaptic currents (EPSCs) and AP-independent miniature excitatory postsynaptic currents (mEPSCs), as well as inhibitory postsynaptic currents (IPSCs) and miniature inhibitory postsynaptic currents (mIPSCs). These types of recordings can identify putative changes in the functional balance between excitatory and inhibitory networks and relate them to discovered phenomenon of enhanced LTP.

SLICE PREPARATION

3X CHI or 3X Sham-injured mice, 7-8 weeks old, were anesthetized with isoflurane, decapitated, and the brain rapidly removed and placed in ice cold ($\sim 4^{\circ}\text{C}$) high-sucrose ACSF cutting solution containing (in mM): sucrose, 206; NaHCO_3 , 26; D-glucose, 10; MgSO_4 , 2; $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, 1; NaH_2PO_4 , 1.25; KCl, 2; CaCl_2 , 1, bubbled with a mixture of 95% O_2 / 5% CO_2 . Parasagittal slices, 400 μm thick, were cut with a Leica VT1200S vibrating blade microtome, and immediately transferred to a warmed ($\sim 34^{\circ}\text{C}$) solution of whole-cell recording ACSF containing (in mM): NaCl, 126; sucrose, 20; NaHCO_3 , 26; D-glucose, 10; KCl, 3; NaH_2PO_4 , 1.25; MgSO_4 , 2; CaCl_2 , 2, bubbled with a mixture of 95% O_2 / 5% CO_2 . After 30 minutes, the slices were transferred to room

temperature ($\sim 21^{\circ}\text{C}$), where they were maintained for at least 1 hour before recording, while continuously being bubbled with 95% O_2 / 5% CO_2 .

ELECTROPHYSIOLOGICAL RECORDINGS

Whole-cell patch-clamp recordings of cells located in area CA1 were performed seven days after the final CHI or sham injury. Using a Hamamatsu C2400 CCD IR camera, cells located in area CA1 were identified, and a whole-cell patch-clamp configuration was obtained with a borosilicate patch pipette of resistance 3-5 $\text{M}\Omega$ containing (in mM): Cesium hydroxide, 135; Gluconic acid, 135; MgCl_2 , 10; EGTA, 1; HEPES, 10; Mg^{2+} -ATP, 2; Na^{+} -GTP, 0.2; CaCl_2 , 0.1; QX-314, 2; pH=7.3. The combination of cesium gluconate and QX-314 permits the cell to be held at more depolarized levels without creating the risk of generating breakthrough action potentials during recordings. We used an ATP-regenerating intracellular solution, which enables longer recording times while maintaining accurate measurements of neural activity (47; 99; 167). For the spontaneous excitatory postsynaptic current protocol, five minute duration recordings were performed in gap-free voltage-clamp mode, with the holding potential set at -55 mV, the approximate reversal potential for chloride. For the spontaneous inhibitory postsynaptic current protocol, five minute duration recordings were performed in gap-free voltage-clamp mode, with the holding potential set at 0 mV, the approximate reversal potential for cations. The miniature excitatory and inhibitory postsynaptic current protocols were the same as the spontaneous current protocols, except that 1 μM tetrodotoxin (TTX) was added to the standard ACSF. At this concentration, TTX blocks voltage-gated sodium currents, and renders all neurons in the entire slice incapable of firing action potentials. This ensures that activity only recorded with TTX is

action potential-independent in nature, and reflects only the spontaneous, (i.e., vesicle release is not evoked by action potentials) quantal release of presynaptic neurotransmitter vesicles

RESULTS OF THE SPONTANEOUS EXCITATORY POSTSYNAPTIC CURRENT EXPERIMENTS

Referring to Figure 6, 3X CHI alters spontaneous excitatory postsynaptic currents (sEPSCs) one week after the final injury. CA1 pyramidal neurons were whole-cell patch clamped with a cesium gluconate intracellular solution, along with the drug QX-314 (2 mM). Representative traces (Figure 6A) show increased frequency of events for the 3X CHI cells, while the 3X Sham cells exhibit larger peak amplitudes. The cumulative probability plot (Figure 6B) demonstrates an increased sEPSC frequency for the 3X CHI cells, which is consistent with an increase in excitatory drive in the CA1 neurons. The sEPSC peak amplitude is decreased in the 3X CHI CA1 pyramidal neurons (Figure 6C). This may suggest an attenuation of the signal due to activity-dependent shunting of current in the distal GABAergic receptors, and/or a deficit in the readily releasable pool of the glutamate-containing vesicles, and/or mechanism related to release of different vesicle pools (97; 159; 281; 481; 488; 489). Because the intrinsic properties experiments demonstrated that the resting membrane potential, membrane resistance, and membrane tau are all unchanged, it is less likely that the triple-injured CA1 neurons have an increase in shunting of current in the proximal GABAergic synapses. Likewise, the decreased charge transfer (Figure 6C) can be explained through similar mechanisms as observed in the sEPSC peak amplitude. In addition, the action potential amplitude was larger for the 3X CHI cells, while the half-width was smaller. These reciprocal changes thereby offset each other, so we do not suspect a change in magnitude of depolarization in presynaptic

neurons, but it is still possible that a change in presynaptic glutamate release could occur. It should be noted that the results of PPF experiments are consistent with unaltered glutamate release from the Schaffer collateral afferents but Schaffer collaterals are not the only afferents that terminate on CA1 pyramidal neurons (Figure 4). There were no changes in the maximum rise time (Figure 6D), but subtle changes in the maximum decay time (Figure 6E). In order to assess directly a potential impact of increased shunting currents on amplitude and kinetics of sEPSCs whole-cell recordings in the presence of GABA_A receptor antagonists should be performed in the future studies.

RESULTS OF THE MINIATURE EXCITATORY POSTSYNAPTIC CURRENTS EXPERIMENTS

Referring to Figure 7, 3X CHI alters miniature excitatory postsynaptic currents (mEPSCs) one week after the final injury. Representative traces (Figure 7A) show the 3X CHI cells exhibit both an increased frequency of events and larger peak amplitudes. Cumulative probability plots (Figure 7B) display an increased mEPSC frequency, which is consistent with an increase in the number of glutamatergic postsynaptic synapses and/or diminish probability of glutamate release. An increase in axonal sprouting during the post-injury restoration phase would also be consistent with these results, thereby leading to an increase in the number of excitatory glutamatergic synapses onto CA1 pyramidal neurons. The increase in peak amplitude (mV) (Figure 7C) suggests that there are more functional AMPA receptors on postsynaptic sites, and/or that the action potential (AP)-independent synaptic vesicles have a larger content of glutamate. The increased charge transfer (Figure 7D) also reflects these changes. Likewise, the changes in time course of mEPSCs also provide evidence that an attenuation shunting effect and/or dendritic filtering are less likely because the decrease in the rise time and increase

in the amplitude have been observed. Therefore, the decreased maximum rise time (Figure 7E), and increased maximum decay time (Figure 7F) suggest changes in the subunit composition of glutamatergic AMPA and/or kainate receptors. The types of AMPA receptors consistent with these results are Ca^{2+} -permeable GluA2 subunit-lacking AMPARs. In addition, changes in posttranslational modifications of AMPAR subunits can also affect excitatory responses (606).

RESULTS OF THE SPONTANEOUS INHIBITORY POSTSYNAPTIC CURRENT EXPERIMENTS

Referring to Figure 8, 3X CHI alters spontaneous inhibitory postsynaptic currents (sIPSCs) one week after the final injury. Similarly to sEPSCs, sIPSCs represent a mixture of both somatic and dendritic inputs; and furthermore, are a more sensitive measure of synaptic inhibition (245). Representative traces (Figure 8A) show both increased frequency of sIPSCs and larger peak amplitude for the 3X CHI cells. The cumulative probability plot (Figure 8B) shows that the 3X CHI pyramidal neurons demonstrate increased sIPSC frequency. This increase in frequency is consistent with the increased frequency observed in the sEPSC recordings (Figure 8B), which showed increased excitatory drive and activity of excitatory neurons, which are likely driving activity of inhibitory neurons. However, the peak amplitude (Figure 7C) is decreased, which suggests a role for activity-dependent shunting of current at the distal glutamatergic synapses, and/or a deficit in the activity-dependent neurotransmitter (GABA) vesicle release (298; 590). The charge transfer (Figure 8D) is likewise decreased. Similarly to sEPSCs results, we can also speculate here that proximal shunting is less likely a contributor here, because the passive properties (Table 1) are unaffected by 3xCHI. The kinetics parameters of spontaneous IPSCs are affected by 3X

CHI. The decreased maximum rise time (Figure 8E) and decreased maximum decay time (Figure 8F) suggest changes in postsynaptic GABA_A receptor subunit composition, and would not be consistent with contribution from the shunting of these currents.

RESULTS OF THE MINIATURE INHIBITORY POSTSYNAPTIC CURRENTS EXPERIMENTS

Referring to Figure 9, 3X CHI alters miniature inhibitory postsynaptic currents one week after the final injury. Representative traces (Figure 9A) show a larger peak amplitude for the 3X CHI CA1 pyramidal neurons, while they also exhibit a slight reduction in frequency of mIPSCs. The cumulative probability plot (Figure 9B) shows that the 3X CHI cells demonstrate decreased sIPSC frequency, which is consistent with a lower number of GABAergic synapses (e.g., the pruning of GABAergic afferents) and/or reduced probability GABA release. However, the increased peak amplitude (Figure 9C) suggests an increase in the number of functional GABA_A receptors within the synapse, and/or a larger content of GABA neurotransmitter in a specific pool of AP-independent GABA synaptic vesicles. We can speculate that the decreased frequency of mIPSCs/pruning effect, coupled with the increase in peak amplitude, serves to offset the reduction in inhibitory drive so both effects tend to compensate each other. Moreover, the increased charge transfer (Figure 9D) reflects the increase in peak amplitude, and also suggests stronger GABAergic synapses / more permeable GABA_A receptors, or a larger content of GABA neurotransmitter contained within a specific pool of action potential independent synaptic vesicles. Therefore, the decreased maximum rise time (Figure 9E), and together with subtle changes in maximum decay time (Figure 9F) rather suggest changes in the subunit composition of GABAergic receptors (37; 70; 199; 234; 298; 357; 456; 534; 574; 600), however, changes in posttranslational modifications of GABAR

subunits can also modulate inhibitory responses (203; 579). Dendritic excitability in CA1 pyramidal neurons is governed by tonic inhibitory currents that are regulated by the $\alpha 5$ and δ subunits of the GABA_AR (70; 199; 217; 357; 456; 574; 600). It may be that 3X CHI promotes the transient expression of dendritic GABA_ARs that lack the $\alpha 5$ and δ subunits, one week after the final injury.

In summary, the changes in the time course of the mEPSCs and mIPSCs collectively suggest that changes in shunting mechanisms are less likely after 3X CHI, because the rise time of the mEPSCs and mIPSCs are shortened and the amplitude is increased. Interestingly, as it will be elaborated in the Discussion, augmentation of the shunting inhibition mechanism have been recently implicated in electrophysiological studies with rodent models of TBI (245; 250; 409; 443). Shunting inhibition refers to the augmented ion conductance that results from the activation of GABA_ARs (443; 444; 596). In CA1 pyramidal neurons, shunting inhibition can alter the input-output relationship by creating offset, but has no effect on the gain (443; 444; 596). Moreover, some evidence for changes in subunit composition of both AMPA and GABA_A receptors following TBI have been also unraveled (183; 290; 409) and are presented in the Discussion. In addition, based on immunohistochemical studies, microglia-mediated changes in excitatory and inhibitory afferents have been previously proposed (155; 437; 492; 493; 515; 559). However, physiological studies directly addressing impact of TBI on a vesicle-pools and/or presynaptic release mechanism are still lacking.

CHAPTER Six: Discussion

NOVELTY OF RESULTS

To our knowledge, this is the first study to observe enhanced hippocampal LTP one week after a triple closed-head injury. Whole-cell patch-clamp recordings revealed alterations in four of the eight active intrinsic membrane properties. CA1 neurons from the triple-injured mice exhibited slightly larger action potential amplitude, shorter half-width, and increases in both maximum rise and maximum decay slopes. These results are consistent with increase in voltage-dependent sodium and potassium currents. At the same time AP frequency responses, AP threshold and resting membrane potential appear to be not affected by 3xCHI. Voltage-clamp recordings provided further evidence that CA1 pyramidal neurons ipsilateral to the injury displayed a fine functional shift between excitatory and inhibitory inputs. The increased frequency and decreased amplitude and charge transfer of the spontaneous excitatory postsynaptic currents suggest that there was an increase in excitatory drive in CA1 pyramidal neurons ipsilateral to the injury. In addition, the miniature excitatory postsynaptic currents exhibited increases in frequency, amplitude, and charge transfer. These results suggest more numerous excitatory synapses and/or increases in probability release of glutamate, and increase in cationic permeability of synaptic AMPARs. They also suggest that excitatory synapses could be more depolarized and therefore exhibit weaker Mg^{2+} block of NMDARs. The spontaneous inhibitory synaptic currents of CA1 pyramidal neurons ipsilateral to the injury demonstrated an increase in frequency, while the amplitude, charge transfer, rise time, and decay time were all decreased. The small increase in frequency of spontaneous IPSCs can be explained by increased activity of excitatory neurons, while changes in

amplitude can be explained by increase in tonic inhibition and/or changes in AP-driven vesicle pools. However, the CA1 neurons displayed opposite changes in their miniature inhibitory postsynaptic currents, where the frequency and rise time are decreased, while the amplitude, charge transfer, and decay time are all increased. The change in frequency of mIPSCs would be consistent with less numerous inhibitory synapses and/or decrease in probability release of GABA, and increase in anionic permeability of synaptic GABARs (stronger inhibitory synapses). In summary, these results are consistent with significant but complex changes involving intrinsic active electrophysiological properties and excitatory and inhibitory synapses following 3X CHI. These alterations lead to functional changes that impact AP characteristics, and may shift the balance between excitatory and inhibitory inputs of CA1 neurons ipsilateral to the injury, with the neurons exhibiting an increase in excitability drive and impaired inhibitory activity. These changes may be accounted for by alterations in subunit composition of both synaptic AMPA and GABA receptors and be linked to increase in LTP, see below for more detailed discussion and considerations.

EXPERIMENTAL DESIGN AND ITS RELEVANCE FOR MODELING RTBI

The first paragraph of Chapter Two described the key elements that an animal model of rTBI should possess in order to effectively represent the clinical manifestations of human rTBI. The cumulative effect of the repetitive impacts has a greater influence on poor outcome than the magnitude of the blunt force trauma (14; 306; 380; 461; 537; 592). The impact coordinates, injury type (closed-head with no craniotomy), velocity of impact (4 m/s), dwell time (100 ms), and caliber of impactor tip (5 mm) were all chosen to create a mild TBI. The time interval between impacts (one CHI every 24 hours) was

selected so that the ipsilateral hippocampus, and its blood supply, would sustain a subsequent injury before full recovery from the previous injury was complete. The time of recordings (seven days after the final injury) was selected because the mNSS-r scores (data generated by the Dr. Neil Grunberg laboratory and Dr. Ranjana Verma of the Galdzicki laboratory) was still significantly elevated. As was previously stated in Chapter Two, it is possible to observe electrophysiological changes coupled with cognitive/behavioral dysfunction when the temporal window of vulnerability is modeled optimally for rTBI (20; 171; 244; 313; 391; 392; 460; 463; 506).

In both behavioral and electrophysiological tests conducted seven days after the final injury, the mNSS-R scores in 3X CHI mice were significantly elevated (~ 2-fold; Figure 2). Likewise, LTP was significantly enhanced in 3X CHI hippocampal slices ipsilateral to the injury but was not significantly altered in 1X CHI hippocampal slices (Figure 3). While not significantly altered, paired-pulse facilitation of Schaffer collateral afferents was observed in the 3X CHI ipsilateral hippocampal slices (Figure 4), there were no significant differences between the 1X CHI ipsilateral, 1X CHI contralateral, 1X Sham-injured, 3X CHI ipsilateral, 3X CHI contralateral, and 3X Sham-injured groups. Moreover, whole-cell patch-clamp recordings of CA1 pyramidal neurons demonstrated that 3X CHI mice exhibited significant changes in active intrinsic membrane properties (Figure 5), sEPSCs (Figure 6), sIPSCs (Figure 7), mEPSCs (Figure 8), and mIPSCs (Figure 9).

As was discussed in Chapter Two, the results of the fear-conditioning tests strongly suggest that hippocampal function is likely impaired during the first week after the final injury. These data generated by the behavioral tests provide further rationale for

conducting electrophysiological recordings one week after the final injury and would further suggest that increased LTP is not due to regain of function.

rTBI CAUSES CHANGES IN CA1 HIPPOCAMPAL FUNCTION

Several rodent studies have been initiated to observe electrophysiological changes caused by a single TBI, and they have reported alterations in excitability in CA1 pyramidal neurons that are ipsilateral to the single injury (90; 141; 196; 315; 431; 432; 595; 612; 613). Six of these rodent single TBI studies reported increased excitability of CA1 neurons post-TBI (90; 141; 196; 315; 431; 432), but only one project modeled a closed-head injury (weight drop), and the animals used in this closed-head model were 11-15 day old postnatal Wistar rats (196). To our knowledge, there is only one very recently published electrophysiological study on repetitive mTBI (20), and this project used adult male Sprague-Dawley rats, 10-12 weeks old, that sustained either single or triple lateral fluid percussion injuries, after craniotomy surgery. Recording 28 days post-TBI, enhanced LTP was observed in the single-injured rats (compared to sham-injured), but LTP could not be achieved in the repetitive TBI animals at this time point (20).

Our present study using a novel mouse model of rTBI found changes in synaptic plasticity expressed as enhanced LTP one week after repetitive injury in mice, which has not been previously reported. In addition, we found that rTBI also causes impairments in behavioral performance. The use of patch-clamp recordings allowed us to gain novel insight into intrinsic functional mechanisms that were impacted by repetitive injury. We found that pyramidal CA1 neurons not only exhibit enhanced synaptic plasticity but also changes in action potential characteristics, which was expressed by larger action potential amplitudes (~5% increase, Figure 5), with accompanying increase of maximum

rise time/depolarizing rate (~8%, Figure 5) and increase in decay time/repolarizing rate (~8% increase, Figure 5). These alterations lead to a decrease in action potential width. These changes in active intrinsic membrane properties are consistent with significant increases in voltage-dependent sodium and potassium currents, which underlie the action potential. Future studies should pharmacologically isolate and measure these currents using voltage-clamp recordings following 3X CHI.

Yeun et al., (609) conducted a study to determine if the poor outcome of rTBI patients is the result of accrued damage from multiple impacts, or if each individual impact contributed to electrophysiological changes that leaves rTBI patients vulnerable to progressive cognitive decline (609). Utilizing a cell culture model of repetitive traumatic axonal injury (rTAI), they observed that a single injury caused an increase in the expression of voltage-gated Na^+ channels along the axons that were otherwise morphologically unremarkable (609). However, a second subsequent injury caused a pathological increase in voltage-dependent sodium current in TTX-sensitive Na^+ channels, which in turn promoted an increase in intracellular Ca^{2+} (609). The key finding of the Yeun et al., study was that this rise in intracellular Ca^{2+} , as a consequence of the trauma-induced Na^+ channelopathy, was the cause axonal degeneration leading to TAI. These repetitive injuries initiated the pathophysiological cascade that resulted in TAI (609).

Extrapolating from the findings of Yeun et al., we want to elucidate if the changes in active intrinsic properties caused by 3X CHI in the mouse model resulted from voltage-gated ion channelopathies. We can speculate that changes in the hippocampus ipsilateral to the injury are responsible for likely increases in voltage-dependent Na^+

current (Figure 5C, increased maximum rise slope) as well as likely increases in voltage-dependent K^+ -current (Figure 5D, increased maximum decay slope). Therefore multiple impacts and selected temporal window between impacts in our model of rTBI yielded worsened outcome, which is consistent with the results of the Yeun et al., *in vitro* cell culture study of rTAI (609).

ENHANCED LTP DOES NOT CORRELATE WITH A RECOVERY OF FUNCTION

Our study is the first to demonstrate enhanced LTP and impaired spatial memory in an animal model of rTBI. Since 1X CHI did not yield any significant differences in percent slope change of LTP when compared to the 1X Sham group, perhaps the multiple impacts are required to create this enhanced long-term plasticity. Power analysis of single CHI suggest that the insignificant increase observed following this injury would require $N=39$ in each group to become significant at $p=0.05$. This outcome strongly suggests that repetitive injury additive and/or synergistic effects produce significant augmentation of LTP in our model of 3xCHI.

Interestingly, other animal models of neurological disease and disorders have also reported augmented LTP coupled with cognitive/behavioral deficits. Experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis, facilitates the enhancement of LTP by promoting the increased release of IL- 1β by activated microglia and invading lymphocytes (136; 402; 417; 418). Moreover, the progression of EAE, demonstrated by decreased clinical scores, correlates with augmented LTP over long-term depression (LTD) in the affected mice (136; 402; 417; 418). To be sure, EAE and our mouse model of rTBI are two very different studies of neurological impairment. However, the enhanced LTP observed in the 3X CHI may possibly be the result of a

cytokine-mediated neuroinflammatory mechanism, driven by the microglia that were activated by repetitive head trauma. In fact, our latest results of immunohistochemical experiments are consistent with region-specific microglia activation following 3xTBI in weeks and months after injury (data not shown).

In this regard, of clinical relevance is the observation of enhanced LTP in human multiple sclerosis (MS) patients (403). Employing transcranial magnetic stimulation (TMS) over the motor cortex, Mori et al., employed a theta-burst protocol to demonstrate that LTP is favored in stable relapse-remitting MS patients, while patients afflicted with the primary progressive form of MS were unable to evoke LTP, but with no longitudinal axonal remodeling (403). A key finding of their study is that platelet-derived growth factor (PDGF) is necessary to evoke LTP in the relapse-remitting MS patients, and they suggest that a possible treatment of MS would be to target PDGF signaling in MS patients (403).

The molecular signaling pathways that drive hippocampal LTP have also been the focus of animal studies of enhanced synaptic plasticity coupled with impaired learning and memory. While it is well known that CREB phosphorylation is needed for the formation of hippocampal-dependent spatial memory (277-279), a transgenic mouse study reports that chronic enhancement of CREB obstructs the retrieval of spatial memories (578). Another transgenic mouse study observed yet another example of constitutively active signaling pathways that result in impaired learning and memory. Viosca et al., reported that when G_s -alpha is constitutively active the cAMP/PKA pathway becomes dysregulated to the degree that despite enhanced synaptic plasticity,

these transgenic mice demonstrated deficits in spatial memory, cued-fear conditioning tests, and contextual fear conditioning (62).

Given the findings from this diverse array of studies, it is possible the mechanisms driving the enhanced LTP in our mouse model of rTBI could share similarities with any of these animal models of increased synaptic plasticity coupled with deficits in learning and memory. However, we propose that future studies should focus on the possible role of neuroinflammation in creating this enhanced LTP, which may in turn lead to the activation of the PKA/CREB pathway. In addition to the roles that neuroinflammation plays in enhanced synaptic plasticity in EAE and MS (136; 402; 403; 417; 418), repetitive head trauma may also activate microglia (136; 402; 403; 417; 418). Activated microglia can produce changes in the degree of pruning/sprouting of axon collaterals and synaptic pruning/formation (155; 283; 439; 470), and/or impact subunit compositions of glutamate receptors in the activated microglia leading in turn to temporal or chronic release of cytokines and neuroinflammatory molecules (43). We can further hypothesize that signs of activated microglia point to changes in neurovascular units and therefore their putative activation (82; 258). Whether and how activated vascular units impact pre- and postsynaptic neuronal components/receptors and microvasculature remains to be determined in the future studies. However more detailed analysis of spontaneous activity obtained in patch-clamp experiments presented below suggests a differential effect by rTBI on the subunit compositions of synaptic AMPA and GABA receptors.

DIFFERENTIAL REGULATION OF THE SUBUNITS OF GLUTAMATERGIC AND GABAERGIC RECEPTORS: A POSSIBLE MECHANISM FOR RTBI-INDUCED CHANGES IN HIPPOCAMPAL CIRCUITRY

The CA1 pyramidal neurons synapses that include the Schaffer collaterals CA3-CA1 and also local synapses within the CA1 field are the most meticulously studied synapses in the CNS (215; 476). The delicate and complex balance between excitation and inhibition at the CA1 synapses is tightly regulated by the types and density of ionotropic AMPA and GABA receptors (277; 279; 299; 365; 573), the subunit composition of those receptors (56; 215; 252; 277; 335; 351; 362; 445; 476; 518; 524; 526; 604), and the gene expression and alternative splicing of the receptor subunits (277-279; 445; 476; 477). At the CA1 pyramidal neuron synapses, the “fast” early component of postsynaptic signaling is produced by the cationic current (predominantly Na⁺ and possibly Ca²⁺ due to their electrochemical gradients) flowing through the AMPAR (Figure 11A) (252; 277; 335; 445; 558). In the following paragraphs we will try to explain that the alterations in Schaffer collateral synaptic plasticity and spontaneous activity of CA1 pyramidal neurons observed in our mouse model of rTBI may have resulted from changes in AMPAR density, AMPAR subunit composition, and AMPAR-mediated cationic current. We also present evidence for possible changes in GABAergic receptors.

AMPA Subunit Composition Determines Its Biophysics and Kinetics

The structure of the AMPAR heteromer is created by the association of four subunits, GluA1-4 (previous nomenclature was GluR1-4, or GluR-A to -D) (140; 233; 252; 277; 335; 364; 498). The various combinations of these subunits determine the biological functions of the AMPAR (119; 252; 261; 335). The AMPAR subunits

principally expressed in the hippocampus are GluA1 and GluA2, while GluA3 and GluA4 are expressed to a lesser extent (115; 179; 252; 395; 484; 560). The key subunit that dictates the magnitude and kinetics of the AMPAR conductance is the GluA2 subunit (215; 252; 277; 335; 445; 518).

The GluA2 subunit is the most strictly governed of all of the glutamate receptor subunits (252). Therefore, we can speculate that our observations in the 3X CHI model may be explained by changes in the quality and/or quantity of GluA2 subunit in hippocampal CA1 pyramidal neurons (77; 160; 181; 226; 252; 257; 477; 505). The GluA2 subunit governs neuronal excitability by curbing the ionic conductance of the AMPAR via an additional positive charge at position 607 of the M2 membrane loop (252; 520). The enzyme adenosine deaminase carries out RNA editing in the pre-mRNA of GluA2, by hydrolyzing an adenosine base to an inosine, which in turn translates to an arginine residue at position 607 where a glutamine was originally encoded (226; 252). This “Q/R editing” endows the GluA2 subunit with the ability to render the AMPAR impermeable to Ca^{2+} , and decreases the ion conductance of the AMPAR, such that the current-voltage (I-V) relationship of the receptor is linear (61; 252; 262; 542; 576). The AMPAR subunit composition displays a “two or none” subunit combination, such that the AMPAR will contain either 2 GluA2 subunits, or will be completely devoid of any GluA2 subunits (74; 195; 252; 354).

Subunit Composition, Location, and Kinetics of AMPARs on CA1 Pyramidal Neurons

AMPARs have a critical role in the induction of CA1 LTP, and both their conductance and kinetics are directly correlated to the precise subunit composition that comprise the AMPARs on CA1 pyramidal neurons (56; 115; 119; 215; 252; 257; 328;

335; 350; 351; 433; 445; 451; 476; 477; 484; 560; 573; 601; 604). When AMPARs contain the GluA2 subunit, synaptically-evoked Ca^{2+} entry is dependent upon NMDARs and voltage-gated Ca^{2+} channels (252; 277). However, AMPARs that lack the GluA2 subunit also lack the positively-charged arginine at position 607 in the M2 membrane loop; therefore, these AMPARs conduct both Na^+ and Ca^{2+} across the neuronal membrane and are integral in CA1 synaptic plasticity and neuronal activity (215; 252; 335; 351; 362; 445; 476; 477; 518; 604).

GluA2-containing AMPARs (i.e., GluA1-GluA2 heteromers) comprise approximately 80% of all synaptic AMPARs, as well as 95% of somatic extrasynaptic AMPARs on CA1 neurons, with the remaining GluA2-containing AMPARs of the GluA2-GluA3 variety (335). Another key finding observed by Lu et al., was that the number and subunit composition of synaptic NMDARs remained constant, NMDAR-mediated EPSCs were unchanged, and NMDAR presynaptic properties were unaffected by a complete absence of AMPARs (both synaptic and extrasynaptic) (335). Moreover, no significant changes in CA1 dendritic morphology were detected, which further suggests that GluA1-GluA2 AMPAR heteromers mediate excitatory synaptic transmission at CA1 pyramidal neurons (Figure 11A) (335).

In addition to the population of GluA2-containing AMPARs, CA1 neurons possess functional GluA2-lacking AMPARs. Numerous recent studies have not only confirmed the presence of GluA2-lacking AMPARs on CA1 pyramidal neurons, but that these Ca^{2+} -permeable AMPARs are essential for activity-dependent synaptic plasticity and hippocampal LTP (Figure 11A) (56; 215; 252; 351; 362; 445; 451; 476; 477; 518; 604). Homeostatic synaptic plasticity (HSP) is the ability of a neuron to manage its own

excitability in comparison to the overall activity of the hippocampal network (518). A proposed mechanism for HSP is synaptic scaling, a type of plasticity that permits CA1 neurons to govern their overall action potential firing rates (534; 535). GluA2-lacking AMPARs participate in HSP in CA1 neurons, via synaptic scaling, and are found at synapses, extrasynaptic dendritic sites, and even at the soma of CA1 neurons (518; 534; 535). These Ca^{2+} -permeable, GluA2-lacking AMPARs on CA1 neurons are further distinguished by their locations: synaptic (119; 178; 200; 214-216; 252; 256; 294; 351; 445; 451; 476; 477; 518; 540; 549; 550; 562), and extrasynaptic (18; 65; 95; 198; 265; 317; 335; 350; 423; 451; 504; 521).

Interestingly, silencing hippocampal circuits with prolonged exposure to tetrodotoxin (TTX) recruits Ca^{2+} -permeable GluA2-lacking AMPARs at CA1 synapses, which results in a significant increase in mEPSC peak amplitude and surprisingly an increase in hippocampal LTP (294; 351; 445; 518; 540; 562). The known mechanisms underlying trafficking, gating properties of AMPARs and impacting their contribution to synaptic plasticity like transmembrane several immediate early genes such as Homer1a (312; 477), transmembrane AMPA receptor regulatory proteins (TARPs) such as stargazin (152; 287; 606), or AMPAR auxiliary subunits that lack TARPs such as cornichon-2 and cornichon-3 (CNIH-2/-3), (147; 225) or AMPAR accessory protein such as PICK1 (147; 225; 549; 550) cannot easily explain changes that we observed in hippocampal circuitry following rTBI. However we will speculate in the following paragraphs that neuroinflammatory cascade triggered by rTBI can affect either of them and differentially impact GluA2 and GluA1 subunit trafficking and/or their assembly and potentially change the AMPARs contribution to synaptic plasticity and hippocampus-

dependent learning and memory (Figure 11B) (405; 594). Our model depicted in the Figure 11A illustrates uninjured putative CA1 neurons with “typical” excitatory and inhibitory synapses. The excitatory synapse contains AMPARs, which majority are not permeable to Ca^{2+} (but are permeable to other cations as Na^+ and K^+). The electrochemical gradient favors influx of Na^+ into the postsynaptic spine volume.

The inhibitory synapses located on dendritic regions outside excitatory spine contain low affinity GABA_ARs (i.e. GABA_ARs that lack either the $\alpha 5$ and/or the δ subunits), which poorly compete for ambient and spillover of GABA with primary binding sites to the GABA_AR in extrasynaptic location, which have high affinity GABA_ARs that contain either the δ and/or $\alpha 5$ subunits. These extrasynaptic receptors are responsible for tonic inhibition and their activation may reduce probability of inducing LTP (70; 502; 503). We can speculate that in uninjured “healthy” CA1 neurons these extrasynaptic GABA_ARs are critical for adjusting the magnitude of LTP in a context-dependent manner. \

Overall, based on our results we propose that rTBI can induce changes/rearrangements of the synaptic AMPRs and GABA_ARs (Figure 11) and/or other posttranslational modifications (e.g. phosphorylation, ubiquitination), which can increase receptors/channels conductance and/or duration of their open times. As expected, before the triple injury, the excitatory synapses are mostly comprised of AMPARs containing GluA2 receptors that make these receptors non-permeable to Ca^{2+} ; following 3XCHI, excitatory synaptic currents increased, which would be consistent with AMPARs lacking the GluA2 subunit. With regard to inhibitory network, following 3XCHI, the inhibitory synaptic currents become larger as well. This suggests insertion of GABA receptors with

a higher Cl^- conductance at the inhibitory synapses. With regard to intrinsic active properties of CA1 neurons after 3XCHI, the results are consistent with increased voltage-dependent sodium and potassium currents following injury.

Therefore, our data would be consistent with excitatory synapses containing AMPARs lacking GluA2 subunits which would make them permeable to Ca^{2+} and stronger (increased cationic conductances). Inhibitory synapses appear to be stronger as well which may decrease tonic inhibition (through competitive effect on binding GABA neurotransmitter and potential reduction of GABA spillover) and would contribute to augmentation in LTP. Furthermore, possible increases in voltage-dependent Na^+ and K^+ channels would explain changes in AP characteristics (609).

Tumor Necrosis Factor-Alpha (TNF α): Cytokine with Synaptic Plasticity Actions That Are Dependent Upon Receptor Type

TNF α is present in the uninjured, normal brain, but its expression is highest immediately after the brain is subjected to trauma, ischemia, stroke, and infections (458; 557; 584). TNF α is active both as a 26 kDa transmembrane protein, and as a 17 kDa soluble domain that is created by the cleaving actions of TNF α -converting-enzyme (TACE) on the original 26 kDa protein (406; 458). Active as a homomeric trimer in both the 26 kDa and 17 kDa forms (303; 458), TNF α binds to two receptors, TNFR1 and TNFR2 (347; 458). These TNFRs are expressed constitutively by neurons, astrocytes, microglia, and oligodendrocytes (145; 297; 458; 603; 616). In general terms, TNF α binding to TNFR1 elicits a cytotoxic response via its cytoplasmic “death domain” (394; 427; 580), while binding to TNFR2 promotes neuroprotection (166; 427; 580; 603).

Paradoxically, the cytotoxic-associated TNFR1 is the same class of receptor that endows TNF α with its ability to influence hippocampal synaptic plasticity (427; 580).

When TNF α is applied to hippocampal neuron cultures, these hippocampal neurons demonstrate increased expression of AMPARs, via a PI3 kinase-dependent pathway, which in turn influences alterations in AMPAR-mediated excitatory postsynaptic currents in these neurons (32; 427; 534; 535; 580). Moreover, most of these newly expressed AMPARs are the Ca²⁺-permeable, GluA2-lacking class of AMPAR, which places neurons at risk to excitotoxicity (162; 344; 427; 523; 580). TNF α further favors excitation over inhibition in hippocampal neurons by triggering the endocytosis of GABAARs (427; 457; 458; 534; 580).

Differential Regulation of Ionotropic Receptor Subunits by TNF α within the Context of Excitatory and Inhibitory Synapses of CA1 Pyramidal Neurons

Studies using cultured postnatal rat CA1 pyramidal neurons were the first to observe AMPARs being trafficked to the synapse, and that these AMPARs adjusted the synaptic strength by nature of their various subunit compositions (427; 504). The trafficking of ionotropic ligand-binding receptors plays a key role in fine tuning synaptic strength during hippocampal-dependent memory tasks, and thus determines the robustness of memory creation, storage, and recall (32; 33; 38; 427; 485; 486; 562). In following paragraphs we will summarize a set of studies that point at TNF α an important element of neuroinflammatory cascade that affects AMPARs and GABA receptors function and structure.

Effect of TNF α on AMPARs

The manner in which TNF α influences hippocampal synaptic plasticity through its astrocytic-dependent “gliotransmission” (49; 207; 446; 485; 486) will be discussed below. However, synaptic strength can be impacted by TNF α through a mechanism

involving AMPRs composition and their neuronal location (6; 32; 120; 427; 544). $\text{TNF}\alpha$ modulates hippocampal synaptic plasticity by the differential regulation of assembly and trafficking of AMPR subunits (45; 185; 317; 394; 422; 427; 534; 591; 608). Hippocampal neurons express Ca^{2+} -permeable, GluA2-lacking AMPARs (265; 317; 422; 451; 553). Using an NF-kappaB-dependent mechanism, $\text{TNF}\alpha$ stimulates the expression of the GluA1 subunit which can make neurons to become susceptible to excitotoxicity (427; 608). When $\text{TNF}\alpha$ binds to the TNFR1 on hippocampal neurons, the excitatory drive is enhanced by increasing the number of synaptic Ca^{2+} -permeable GluA2-lacking AMPARs and by endocytic removal of surface GABA_A Rs (427; 534; 535). This $\text{TNF}\alpha$ mediated-upregulation of Ca^{2+} -permeable GluA2-lacking AMPARs occurs within 15 minutes of exposure to $\text{TNF}\alpha$ (317; 422; 534; 535). Another study replicated these results, and also observed that this accelerated expression of Ca^{2+} -permeable GluA2-lacking AMPARs by $\text{TNF}\alpha$ happens through a posttranslational mechanism (422; 427).

Effect of $\text{TNF}\alpha$ on GABA_A Rs

$\text{TNF}\alpha$ has an opposite effect on the inhibitory GABA_A ergic synapses of hippocampal neurons. Binding to the TNFR1 on CA1 pyramidal neurons, $\text{TNF}\alpha$ can reduce inhibitory synaptic strength through a dynamin GTPase-mediated mechanism, resulting in a decreased mIPSC peak amplitude and a corresponding decrease in the mIPSCs frequency (427; 457; 458). Moreover, the GABA_A Rs on the CA1 neurons are promptly endocytosed in response to $\text{TNF}\alpha$ exposure, employing a mechanism that involves the activation of p38 MAPK, phosphatidylinositol 3-kinase (PI3K), and protein phosphatase 1 (PP1) (427; 457; 458).

We then can summarize that differential regulation of ionotropic receptor subunits by TNF α is a possible important contributor to the mechanisms that may produce both the enhanced LTP and changes in excitation and inhibition in our mouse model of rTBI and therefore warrants further considerations in order to reconcile our results with findings related to TBI and/or rTBI (427; 534; 535). One of the most important contributors to underlying neurological deficits that was proposed to be triggered by TBI is either the transient and/or chronic neuroinflammatory response (1; 501; 597).

THE MODULATORY EFFECTS OF NEUROINFLAMMATION ON HIPPOCAMPAL SYNAPTIC PLASTICITY

One of the major secondary injury mechanisms associated with TBI is neuroinflammation, and the hippocampus is distinctly vulnerable to its effects (136). Hippocampal synaptic plasticity is significantly altered by neuroinflammation (136; 137; 197; 221; 390), and field CA1 is particularly susceptible to the deleterious plasticity changes (136; 390). Crosstalk between the CNS and the immune system is so intricate (136; 137) that some neuroscientists consider the neuronal synapse to consist of the pre- and postsynaptic neurons, as well as astrocytes, microglia, and endothelial cells (26; 136; 137; 581). Collectively, these cells comprise the neurovascular unit, and have been observed to modulate synaptic plasticity, particularly the induction of LTP (26; 136; 137; 581). The neuroimmune crosstalk between neurons, astrocytes, microglia, endothelial cells, and invading leucocytes occurs through cytokines; regulatory proteins once thought to have a strictly immune function (26; 136; 137; 581). Cytokines not only influence hippocampal synaptic plasticity during neuroinflammation, but they also maintain the synchronicity of the crosstalk between the cells of the neurovascular unit in the healthy, uninjured brain (21; 40; 48; 49; 136; 137; 458; 496; 605). This diverse and intricate

influence that neuroinflammation exerts on hippocampal synaptic plasticity necessitates a thorough discussion of its possible role in the enhanced LTP that was observed in our mouse model of rTBI.

Pro- and Anti-inflammatory Actions of TNF α

Once classified as strictly a proinflammatory cytokine, TNF α has been shown to exert either a detrimental or neuroprotective effect based on the receptor type, its concentration, and its duration of action (486). The proinflammatory properties of TNF α are typically associated with the “early” phase of inflammation (i.e., within hours of the primary injury) (224; 618). These deleterious actions of TNF α include the increased production and hypertrophy of microglia, which reciprocally stimulates the increased release of TNF α (224; 618). Furthermore, TNF α mediates leucocyte recruitment from the peripheral circulation and the release of blood-brain-barrier-degrading proteases, thereby further compromising the integrity of the BBB (128; 224; 295; 385). TNF α also potentiates the inflammatory response by synergistically augmenting the neurotoxicity of IL-1 β (8; 9; 100; 618).

Conversely, studies involving knockout mice for TNF α suggest that it has anti-inflammatory and neuroprotective effects long after the initial neuroinflammatory response (224; 494; 539). Specifically, these mice that lack TNF α demonstrated greater neurodegeneration, BBB damage, and a poorer outcome when compared to WT mice (44; 224; 494; 539). These data suggest that TNF α plays a critical part in exacerbating the acute phase of the neuroinflammatory response, while displaying some neuroprotective or adaptive properties in longitudinal TBI studies (224; 494; 539).

TNF α Alters Hippocampal Synaptic Plasticity by Increasing the Frequencies and Amplitudes of Miniature Excitatory Postsynaptic Currents

Santello et al., first reported that microglial-released TNF α promotes glutamatergic neurotransmission by increasing glutamate release from astrocytes (485; 486). Microglia activated by the primary impact release greater amounts of TNF α , which bind to TNFR1's on astrocytes (485; 486). This microglia-mediated, astrocyte-dependent form of synaptic plasticity has been termed "gliotransmission" (49; 207; 446; 485; 486). By binding to and activating astrocytic TNFR1's, TNF α induces an increase in astrocytic intracellular Ca²⁺ through signaling pathways that involve prostaglandins and the C-X-C chemokine receptor 4 (CXCR4) (49; 207; 446; 485; 486). These TNF α -enhanced intracellular signaling pathways magnify the effect of the chemokine CXCL12 binding to the CXCR4 receptor, which in turn is responsible for the increase in astrocytic intracellular Ca²⁺ (49; 207; 446; 485; 486). This increase in intracellular Ca²⁺ leads to the amplification in astrocytic glutamate release, and at pathological concentrations TNF α causes a level of astrocytic glutamate release that far exceeds that of any CXCR4 agonist (49; 485; 486). Interestingly, this increase in astrocytic glutamate release activates presynaptic NMDARs, which thereby contributes to both synaptic strengthening and increased glutamate release by the presynaptic neuron (135; 264; 485; 486).

The collective effect of TNF α -mediated, astrocytic-dependent gliotransmission is best observed in whole-cell voltage-clamp recordings of CA1 pyramidal neurons. Treatment of CA1 neurons with exogenous TNF α , ranging in concentrations from 0.6-60 nM, for 15 minutes up to 4 hours, all resulted in increased frequency and amplitude of mEPSCs (32; 192; 485; 486; 534; 535; 544). Moreover, field potential recordings CA1 neurons in hippocampal slices that were treated with 1-100 nM of TNF α exhibited

increases in both fEPSP slope and EPSP amplitude (485; 486; 544). Field potential and whole-cell patch clamp recordings of CA1 neurons from TNF α KO and TNFR1KO mice displayed no changes in the frequencies and amplitudes in their mEPSCs, nor any changes in fEPSP slope (6; 282; 485; 486; 585).

Do The Excitatory Effects of TNF α Translate into Enhanced Hippocampal LTP?

Despite the ability of TNF α to potentiate glutamatergic neurotransmission in the hippocampus, this did not translate to an enhancement of hippocampal LTP in the studies that we have reviewed. Moreover, TNF α can inhibit the induction of LTP in the perforant pathway (85; 120; 121; 458; 585). Regarding CA1 Schaffer collateral LTP, TNF α does not seem to prevent its induction. However, while TNF α increased both the expression of GluA1-containing AMPARs and the AMPAR-to-NMDAR current ratio, it did not enhance CA1 Schaffer collateral LTP in the uninjured brain (457; 458; 534; 535). In other words, the actions of TNF α prevents LTP induction in the perforant pathway, but it has neither an inhibitory nor an enhancing effect on CA1 Schaffer collateral LTP in the uninjured brain (85; 120; 121; 457; 458; 534; 535; 585). However, there is recent evidence that TNF α may lower the threshold for LTP induction via its mediating effects of phosphorylation the GluA1 subunits of AMPARs which would be consistent with our results following 3X CHI (212; 457; 458).

Behavioral Studies of the Effects of TNF α on Hippocampal-Dependent Memory

Animal studies on the effects of TNF α on learning and memory have generated number of outcomes(605). However, there have been experiments that report learning and memory deficits associated with TNF α . Daily i.c.v. TNF α administrations for seven days prior to training resulted in spatial memory deficits in the Morris water maze (54;

605). Rats that received intra-hippocampal injections of TNF α demonstrated longer latencies and a greater number of errors in the three-panel runway task, when compared to the performance of controls (361; 605).

Conversely, transgenic mice that overexpress the TNF α gene presented spatial memory deficits only in an age-dependent manner (11; 165; 605). In these particular transgenic strains, TG6074 and TGK3, respectively, hippocampal-dependent spatial memory was not compromised in 30-day-old mice (11; 164; 605). However, 60-day-old TG6074 mice exhibited significant impairments in spatial memory when compared to that of controls (164; 605).

Results from studies involving mice that have the TNF α gene knocked out are particularly varied. Golan et al., observed augmented spatial memory in TNF α KO mice; however, the same mice demonstrated no significant differences from controls in hippocampal-independent memory performance (185; 605). Other strains of TNF α KO mice showed no spatial memory deficits in Morris water maze performance (180; 494; 602; 605). Of particular interest are traumatic brain injury studies with TNF α KO mice. These mice sustained a single controlled cortical impact injury (CCI), and had a more accurate spatial memory performance compared to wild type mice that also sustained a single CCI (494; 605). Therefore, there is a possibility that the enhanced LTP and the observed shift between excitation and inhibition in CA1 pyramidal neurons may be at least in part mediated by TNF α that could be upregulated by rTBI (Figure 12).

Neuroinflammation Affects Vascular Units following TBI

TNF α , IL-1 β , and IL-6 each have been observed to demonstrate effects on the vascularity post-TBI. As was previously stated, IL-1 β exacerbates BBB damage by

upregulating the production of matrix metalloproteases (MMPs) in endothelial cells (224; 399-401). TNF α has a synergistic effect on IL-1 β , and independently mediates the recruitment of leucocytes from the peripheral circulation, and these cells will release BBB-degrading proteases (12; 136; 137; 219; 224; 399-401). IL-6 counters the deleterious effects of TNF α and IL-1 β by inhibiting their respective receptors, and it also promotes revascularization and repair by increasing the production of NGF (12; 136; 137; 219; 224; 399-401). Changes to vasculature following rTBI are actively investigated in Galdzicki Laboratory using techniques that renders whole brain optically transparent.

Global Effects of rTBI: A Functional Shift Between Excitatory and Inhibitory Inputs to CA1 Pyramidal Neurons, The Potential Role of Dendritic Filtering

The recordings of miniature spontaneous excitatory and inhibitory currents demonstrated significant changes in network properties (Figure 10). This E/I shift may have resulted from a decrease in the number of inhibitory synapses with a concomitant increase in the number of excitatory synapses. These global changes are consistent with our hypothesis that rTBI triggers a shift in excitatory and inhibitory postsynaptic currents, which in consequence leads to changes in excitatory and inhibitory networks of CA1 pyramidal neurons that are ipsilateral to the injury.

Further study of this E/I shift could use a refined analysis of the spontaneous and miniature postsynaptic current data for the influence of dendritic filtering. The passive intrinsic membrane properties determine the extent of dendritic filtering that will occur (277; 348; 601). Input resistance will increase with the distance from the soma, while the membrane capacitance increases with the membrane area (348). As a result, inputs from distal dendrites will have smaller amplitudes and decreased velocities at the soma of the

neuron (348; 522; 601). Therefore, temporal summation of inputs from distal dendrites is greater than for inputs from proximal dendrites (348; 522; 601).

Van Sickle and Tietz devised a method to analyze the effects of dendritic filtering in CA1 pyramidal neurons. For the postsynaptic current data, they plotted the rise time and decay time constants against the peak amplitudes for individual events (573). Histograms of the peak amplitudes were fit with Gaussian curves, so to determine if there were multiple populations of peak amplitudes in CA1 pyramidal neurons (573). They compared these histograms of the total number of postsynaptic current events recorded from neurons from treated mice, to the histograms for the control mice, and they were able to demonstrate multiple populations of peak amplitudes in the treated mice (573).

It would be of great value to conduct a dendritic filtering analysis to detect any effects that rTBI may exert on promoting/hindering dendritic filtering in CA1 pyramidal neurons. Furthermore, analysis for dendritic influence would contribute to a better understanding of the underlying mechanisms that drive the pathophysiology of rTBI with respect to neuronal remodeling (i.e., axonal sprouting and dendritic pruning), and possible changes in neuronal microanatomy.

HYPOTHETICAL MODEL OF THE IMPACT OF 3X CHI ON HIPPOCAMPAL CA1 NEURONS

The model proposed in Figure 12 summarizes our findings. This model is based on the literature discussed above and proposes a novel framework for understanding our results. The triple closed-head impacts induce the activation of microglia, which likely release pathological levels of TNF α that bind to TNFR1's on astrocytes (485; 486). By binding to the TNFR1, TNF α can activate a series of signaling pathways that result in increased astrocytic intracellular Ca²⁺ (49; 207; 446; 485; 486), which, in consequence,

could lead to the impairment in glutamate clearance from the synapse (49; 485; 486).

The resultant increase in ambient glutamate in the presynaptic space could explain enhanced activity of hippocampal neurons after injury as indicated by increases in frequency of spontaneous activity (49; 485; 486).

Based on previous reports, we also hypothesize that TNF α can bind to TNFR1s located on CA1 pyramidal neurons, and thereby trigger alterations in hippocampal synaptic plasticity by the differential regulation of AMPAR subunits (45; 185; 317; 394; 422; 427; 534; 591; 608), leading to the insertion of Ca²⁺-permeable GluA2-lacking AMPARs on the postsynaptic membrane (317; 422; 534; 535) possibly via a posttranslational mechanism (422; 427). If this occurs after 3X CHI, this could explain that the enhanced LTP observed in our model may have occurred in a similar manner as the augmented CA1 LTP that was exhibited in GluA2 knockout mice (257; 594). Intriguingly, the GluA2 knockout mice displayed impairments in multiple hippocampal-dependent learning tasks (257; 594). This GluA2-independent synaptic plasticity relies more on PI3/MAP kinases rather than on calcium/calmodulin protein kinase II (CaMKII) signaling pathways (19).

While these referenced studies offer a substantial rationale for the possible role of TNF α -mediated upregulation of Ca²⁺ permeable GluA2-lacking AMPARs in rTBI, there are also a number of studies implicating that TNF α has modulatory effects on the inhibitory GABA_ARs (427; 457; 458). Interestingly, a single CCI study in adult male Sprague-Dawley rats demonstrated strengthened tonic inhibition and changes in synaptic GABA_ARs (70; 290; 302; 409). There are no known studies that observe a direct impact of TNF α on voltage-dependent sodium and potassium currents; however, signaling

pathways that can be affected by TNF α have been shown to modulate these currents (51; 103; 204)

Given the potential association of receptor and channel subunit rearrangement for both excitatory and inhibitory synapses, and neuronal activity with hippocampal-dependent learning and memory, it appears that TNF α emerges as a viable candidate for future studies that focus on the intracellular mechanisms that produced the enhanced LTP, changes in intrinsic activity, and shifts in E/I balance in our mouse model of rTBI (427; 534; 535).

VOLATILE ANESTHESIA DURING SURGERY: POSSIBLE CONFOUNDING VARIABLE

The neuroscience researcher faces a conundrum when designing a repetitive TBI study. Administration of anesthetics to animals undergoing multiple TBI surgeries is not only a required IACUC standard, but it is also an unquestionable component of any humane scientific experiment involving repetitive head trauma to animals. For the electrophysiologist, the pharmacology and chemical properties of an anesthetic may influence the functions of ion channels, ligand-gated receptors, and ultimately the currents flowing through these channels. By altering the function and current flow of ion channels and receptors, an anesthetic could contribute to global changes in synaptic plasticity. Any observed alterations in synaptic plasticity could be misconstrued as the result solely from the rTBI, instead from a combination of effects from rTBI and the anesthetic. The use of volatile anesthetics may mask or enhance any effects that are observed in the treatment group. Other investigators have reported that the pathophysiology and/or outcome of their models of rTBI were confounded by

administering volatile anesthesia during the rTBI surgery (63; 130; 142; 392; 447; 475; 528; 610).

Isoflurane was chosen as the volatile anesthetic for this study, based on its efficaciousness as an anesthetic in previous projects in the Galdzicki laboratory, as well as the data from Statler *et al.* (528-532) regarding use in the rat model. Statler *et al.* demonstrated isoflurane's neuroprotective effects that are only expressed when the drug is administered just before surgery, (528-532) a circumstance unlikely to translate beyond an experimental animal model. Additionally, Sham-injured control groups were used in all injury groups (1X CHI and 3X CHI) in order to normalize as many variables as possible. Isoflurane has been observed to augment cerebral blood flow (316; 529), while decreasing glutamate release (441; 529). Further investigations demonstrated that isoflurane is antagonistic to NMDA receptors (NMDARs), and thereby decreases Ca^{2+} influx through NMDARs (52; 529). Conversely, isoflurane is an agonist to GABA_A receptors (GABA_{ARs}) in hippocampal organotypic cell cultures (53; 529), providing additional evidence that the neuroprotective effect of isoflurane is based upon its ability to decrease the excitability of neurons.

Mitigating the Potential Impact of Isoflurane on Our Results

Any compound that influences neurons and their glutamatergic and GABAergic receptors must be taken into consideration when analyzing electrophysiological data. However, in this study, the animals in both the Sham and CHI groups were exposed to the same quantity and frequency of the drug. By doing so, the influence of isoflurane on the physiology of the CA1 pyramidal neurons would be likely the same between both the CHI and Sham-injured groups.

Based on the statistically significant differences observed between the 3X CHI ipsilateral and the 3X Sham-injured recordings, we believe that the repeated administration of isoflurane did not directly skew our results. Furthermore, for the LTP and paired-pulse facilitation recordings, there were no significant differences between the 3X CHI contralateral and the 3X Sham recordings. Therefore, it can be concluded that the experimental design of our study adequately addresses the possible confounding variables that multiple administrations of isoflurane could create.

DETRIMENTAL IMPACT OF RTBI ON U.S. MILITARY SERVICEMEMBERS

Since the end of the Vietnam War, the United States has maintained an all-volunteer military that comprises less than one percent of the total population of the country. A consequence of this is that Service members serve multiple combat deployments during periods of high operational tempo, which increases both their exposure to enemy fire and the risk of sustaining rTBI. Technological advancements in force protection, including individual Kevlar™ body armor with ceramic plate inserts, and “up-armored” vehicles such as the Mine-Resistant Ambush-Protected vehicle (MRAP), have altered the epidemiology of combat wounds. Compared to combat wounds sustained during the Vietnam War, the current conflicts in Iraq and Afghanistan have generated twice as many head and neck wounds (proportionally), while the incidence of thoracic and abdominal wounds has decreased (39; 64). Moreover, the level of medical care at the infantry squad and platoon level has improved to the degree that the current killed-wounded ratio for American Service members is less than 1 in 10 (64; 324). In basic terminology, more combat veterans survive hostile fire than in previous wars would have brought certain death. However, the repeated exposures to combat via

multiple deployments put Service members at risk of sustaining rTBI (39; 64; 324). The risk that rTBI poses to both combat veterans and active duty Service members evoked a concerted effort by military, civilian, and Department of Veterans Affairs health care professionals to both reduce the incidence of rTBI as well as improve the long-term outcome for rTBI patients (39; 64; 78-80; 228; 230; 324; 379; 449).

From this collective body of work, the heterogeneous nature of military-related rTBI is clear. Combat veterans with a history of at least one TBI are at greater risk for being diagnosed with rTBI following a subsequent head injury (78). Compared to Servicemembers with a history of a single TBI or no incidence of TBI, combat veterans that experience rTBI are not only more susceptible to suffering a future TBI, but they also report an increased severity of psychiatric symptoms and behavioral deficits (15; 78; 80). The total number of TBIs is correlates strongly with sleep disturbances, and actually predicts the degree of severity of future insomnia episodes (79). Chronic insomnia contributes to poor patient outcome in cases of rTBI due to its association with patient noncompliance to treatment plans, functional impairment, and the aggravation of psychiatric symptoms of rTBI (79; 598; 611).

A recent neuroimaging study on military-related rTBI elucidated a possible threshold effect of repetitive blast-TBIs on white matter integrity (449). Combat veterans with a history of repetitive blast/impact TBIs exhibited white matter abnormalities in the corpus callosum, subgyral, longitudinal, and subcortical white matter tracts, in addition to reduced glucose metabolism in the parietal, somatosensory, and visual cortices (449). An association was also revealed between the number of repetitive blast/impact TBIs, compromised white matter integrity, and severity of psychiatric / behavioral symptoms.

Repetitive blast/impact TBI patients had a greater degree of white matter lesions, and they also reported a greater severity of depression, insomnia, substance abuse, and PTSD when compared to controls (449). The prodigious variety of genetic and optically enhanced mouse models will enable a preclinical mouse model of rTBI to address the numerous clinical symptoms of rTBI. Furthermore, a preclinical rTBI mouse model will expedite the advent of novel pharmacological and efficacious interventional therapies to help increase readiness of the troops and subsequently facilitate their successful return to civilian life.

FUTURE DIRECTIONS

Based on the results of hippocampal whole-genome transcriptome analysis (RNA-Seq), data generated by members of the Galdzicki laboratory, future studies should also include cell-specific RNA-Seq and an assessment of expression profiles of up-regulated and down-regulated mRNAs (and their brain specific localization by *in situ* hybridization), following by expression profile of respective proteins, as well as the impact of rTBI on signaling pathways. Immunohistochemistry and EM can be employed to detect the number and density of excitatory and inhibitory synapses. Furthermore, an assessment of the morphology of the dendritic spines (e.g., mushroom, stubby) may yield valuable information on the strength of the synapses. The neurodegenerative time course of this rTBI mouse model should be further characterized. Immunohistochemistry can also quantify the anatomical location, extent and degree of diffuse axonal injury (DAI) also referred to as traumatic axonal injury (TAI).

Future patch clamp experiments should use the neurbiotin-avidin conjugate in the intracellular solution backfilled into the patch pipette. This will allow better verification of the morphology of the patch-clamped cells.

Our mouse model of rTBI can be the focus of longitudinal studies to observe changes in the pathophysiology of rTBI. Specifically, we believe that future projects involving neuroimmunological markers in conjunction with cognitive/behavioral testing will provide valuable insights to neurological impairments caused by rTBI using longitudinal approach aided by MR and PET imaging. Furthermore, this model holds the potential for pharmacological and behavioral therapies for rTBI, with a vast selection of conditional and cell-specific knockout strains that enables the investigation of the underlying mechanisms that drive the pathophysiology of rTBI. Sleep studies could be employed to investigate the role rTBI has in exacerbating the sleep disorders that afflict rTBI patients, particularly in the military community.

COMBINING OPTOGENETICS AND IMAGING TECHNIQUES TO REVEAL THE POTENTIAL CLINICAL RELEVANCE OF THIS THESIS PROJECT

Like all neuroscience techniques, electrophysiology has its limitations. It is a matter of debate that observing the functional electrical activity of individual neurons can generate clinically relevant information about the formation, storage, integration, and retrieval of memories that encompass various networks and diverse regions of the brain (387; 501). The complexity and heterogeneity of TBI, especially rTBI, shows that more basic and preclinical research is required. This research has to address complexity of disorder and utilize new emerging technologies.

However, recent studies combining the techniques of optogenetics and calcium imaging have started to show great promise at generating clinically relevant translational

research. Optogenetics provides “real-time” manipulation of genetically classified neuronal populations (e.g., CA1 pyramidal neurons) in animals actively performing cognitive/behavioral tasks with millisecond precision (46; 161; 188; 436; 614). In other words, optogenetics permits the investigator to clearly define the functions of a particular population of neurons, as well as the network connections between these neurons (46; 161; 188; 436; 614).

Optogenetics has been successfully employed to elucidate the role that field CA1 plays in the formation, storage, integration, and retrieval of fear memories (188; 189). Mice undergoing fear conditioning were unable to form contextual fear memories when CA1 pyramidal neurons were persistently optogenetically inhibited. However, when these same mice were retrained in the absence of optogenetic inhibition of field CA1, the mice were able to form contextual fear memories (188; 189). Conversely, optogenetic excitation of CA1 neurons promotes their disinhibition from inhibitory interneurons, and these dysregulated hyperexcitable CA1 pyramidal neurons are associated with deficits in fear memory (188; 333). Based on the results from these studies, future experiments utilizing optogenetics could reveal the underlying mechanisms of enhanced LTP after rTBI.

The greatest benefit that optogenetics provides to the electrophysiologist is that it is possible to conduct electrophysiological recordings while simultaneously optogenetically controlling the excitation/inhibition of a specific population of neurons in animals actively performing cognitive/behavioral tasks (188; 588). By combining calcium imaging with optogenetic manipulation of neural activity, the investigator is able to characterize the spatiotemporal function of neurons with millisecond precision in “real

time” (i.e., as the animal negotiates a cognitive/behavioral test) (3; 131; 188; 189; 424; 588; 615; 619).

By using an interdisciplinary approach, it soon may be possible to pinpoint how rTBI alters the functional connectivity of neural networks *in vivo*. Moreover, if these changes can be detected and characterized before a patient begins to present with any neurocognitive impairments, the basic science researcher will have provided the clinician with an expanded therapeutic window and refine targets for more effective treatment options to be offered to the rTBI patients.

MINDFULNESS-BASED COGNITIVE THERAPY / ACCEPTANCE AND COMMITMENT TRAINING: PROMOTING RESILIENCE IN NEURAL CIRCUITRY PRIOR TO TRAUMA AND REWIRING DAMAGED NETWORKS POST-TRAUMA

As basic science researchers are elucidating the underlying mechanisms that drive the progression of rTBI, clinicians are concurrently treating rTBI patients by incorporating the mindfulness-based cognitive therapy regimen pioneered by Dr. John Kabat-Zinn (125; 268-274; 340; 359; 386; 389; 442; 491). Mindfulness meditation is a secularized form of the self-compassionate introspection practiced in Buddhism and other Eastern religions (259). Clinicians and scientists have come to appreciate the potential that mindfulness-based acceptance and commitment therapy holds for treating rTBI (5; 22; 34-36; 259; 284; 319; 374; 386; 453). rTBI patients are trained to compassionately accept their current circumstances by learning to remain in the present moment (22; 34-36; 284; 374; 453). Patients gradually acquire a different perspective of their physical and mental deficits, and they gain the confidence to fully participate in each moment of life, despite the severity of their symptoms (5; 22; 34-36; 259; 284; 319; 374; 453).

Empirical Evidence of the Benefits of Mindfulness Training in Treating the Cognitive and Neurobehavioral Deficits Associated with rTBI

Maladaptive coping behaviors to stress and anxiety have been observed to exacerbate the susceptibility to, and the progression of, diseases and aging of the CNS even in the healthy, uninjured brain (154; 266; 276; 285). Mindfulness-based compassion training has demonstrated clinical efficacy against psychological, neurological, neuroendocrine, and neuroinflammatory insults by promoting the rewiring of neural circuitry in the brain (156; 157; 267; 269-276; 301; 341; 345; 474; 495). Neurological symptoms that are heavily associated with rTBI, such as depression, anxiety, impulsivity, sleep disorders, and cognitive impairment all are reduced in symptom severity in response to mindfulness-based cognitive therapies (29; 81; 93; 111; 242; 293; 334; 500; 514; 545).

Mindfulness Training Results in Neuroanatomical and Structural Modifications to Regions of the Brain That Are Susceptible to Damage from rTBI

Neuroimaging studies have been conducted to correlate the improved cognitive and behavioral performances of patients that underwent mindfulness training with any anatomical changes (238; 334). The anterior cingulate cortex (ACC) is a key structure that is integral to executive attention (83; 334), and is vulnerable to rTBI (416). Mindfulness meditation consistently produces significant increases in both the thickness and activation of the ACC (176; 177; 239; 334). Furthermore, mindfulness increases the gray matter density in other rTBI-susceptible areas (416) that include the prefrontal cortex (PFC), and hippocampus (176; 177; 231; 235-239; 334; 337-339; 513; 525). Importantly, mindfulness differentially reduces the activation of the amygdala while increasing the activation of the medial prefrontal cortex (MPFC), ACC, PFC, and the

orbitofrontal cortex (OFC), (75; 118; 138; 255; 334; 393), structures that are integral to the regulation of emotion (27; 186; 220; 334; 421; 582). This differential activation and reduction in brain activity associated with mindfulness training is also accompanied by a reduction in volume in the right amygdala and left caudate, which is consistent with the effect of mindfulness has on enhanced resilience to stress exposure (334; 547).

Mindfulness Meditation Triggers Epigenetic Changes in the Activity of Histone Deacetylases (HDACs) and in the Expression of Neuroinflammatory Genes

The inability of a patient to cope with stress, anxiety, doubt, and uncertainty is associated with poor neurological outcome (154; 266; 276; 285; 301). Independent studies on mindfulness have observed that patients who meditate regularly are better equipped to cope with psychological, neurological, endocrine, and immunological stressors/insults (156; 157; 275; 276; 301; 341; 345; 474; 495). A study on the effects of mindfulness on peripheral inflammation observed that patients who practiced mindfulness demonstrated reduced levels of cytokines, DNA damage, and decreased oxidative stress (92; 276). In another study, HIV-positive patients who underwent an 8-week mindfulness training program exhibited a significant increase in CD4⁺ T lymphocytes (117; 276). Mindfulness has demonstrated beneficial effects when implemented in RNA microarray experiments. These microarray studies reported that mindfulness significantly modulates gene expression in the pathways involved in oxidative stress, cellular metabolic imbalance, NFκ-B inflammatory signaling, and telomerase activity (50; 55; 149; 276; 314).

Graff et al., confirmed that external environmental stimuli induces epigenetic changes in gene expression associated with the stress response and behavior in the brain (191; 276). Building on these findings, Kaliman et al., successfully demonstrated that

mindfulness training causes prompt epigenetic modifications to gene expression to histone deacetylases, and induces the downregulation of pro-inflammatory genes and in genes associated with the cortisol HPA axis (276). Specifically, mindfulness decreased the expression of histone deacetylases 2, 3, and 9 (HDAC 2, HDAC 3, HDAC 9) (276). HDACs 2, 3, and 9 are targets for the anti-neuroinflammatory drugs HDAC inhibitors (HDACi)s (4; 208; 499). Mindfulness offers the distinct advantage over the administration of HDACi:s because it has no pharmacological side effects or potential neuro/cytotoxicity (276). Moreover, the reduction in gene expression of HDACs 2, 3, and 9 produces a downregulation in the pro-inflammatory genes *RIPK2* and *COX2* (276). Finally, the confirmed effect of mindfulness training on the inhibition of the pro-inflammatory NF κ -B pathway (50; 55; 117; 118; 149; 276) suggests that a consistent, longitudinal mindfulness regimen would offer significant benefits at attenuating the cognitive and neurobehavioral deficits associated with neuroinflammation caused by rTBI.

Effects of Mindfulness Training on Hippocampal Volume, Combat Resilience, and Symptom Severity of rTBI, PTSD, and Combat-related Sleep Disorders

Mindfulness-based cognitive therapy has been observed to increase the volume both in the hippocampal head and in the gray matter regions of the prefrontal cortex (168; 338; 339). Moreover, mindfulness training significantly increases the amplitude of the P300 ERP and increases the accuracy of tested subjects (308).

The neurobehavioral symptoms associated with rTBI, particularly depression, anxiety, high-risk behavior, avoidance of stressful situations, and impulsiveness are all significantly reduced in severity as a result of mindfulness training (227; 356).

Independent studies that trained United States Marines in mindfulness prior to combat

deployments reported significantly improved combat resilience when compared to Marines that received no pre-deployment mindfulness training (69; 206; 260). Enhanced combat resilience has also been observed in mindfulness studies that focus on combat infantrymen in the United States Army (116; 464).

The mindfulness studies that hold paramount value are the ones that demonstrate improved patient outcome in individuals who received no mindfulness training prior to suffering trauma. Mindfulness-based cognitive therapy / acceptance and commitment training administered to combat veterans post-trauma demonstrates significant improvement in PTSD symptoms, cognitive outcome, quality of sleep, and in the self-management of combat stress (84; 91; 116; 322; 414; 527). Collectively, mindfulness training offers immense potential in treating rTBI without the side effects commonly associated with neurosurgery and pharmacological therapies.

FINAL CONCLUSIONS

86 years ago, the American pathologist Dr. Harrison Stanton Martland was the first to characterize rTBI as *dementia pugilista* (i.e., “punch drunk”), and documented that its diagnosis can only occur in *post mortem* cases (358; 482). CTE is the current nomenclature for *dementia pugilista* (482) and is the hallmark pathology of rTBI. Additional research is needed to develop an effective diagnosis for CTE in living patients (23; 371; 375-380; 428-430; 447; 448; 533; 536; 537).

This study has generated data that strongly suggests that rTBI creates electrophysiological changes in the field CA1 of the hippocampus, possibly by a neuroinflammatory-associated mechanism. It is highly probable that these alterations in neural activity begin weeks, months, or years before the patient presents with any

symptoms. Furthermore, the electrophysiological changes continue uninterrupted as the outcome of the patient deteriorates. In order to provide the treatment that these rTBI patients need, more work needs to be done at the basic science level, before the results of these works can be translated to the patients' bedside.

Effective therapies for brain disorders will take time to develop and show results. The best way, to do this, is through sustained basic, preclinical and translational research that would lead to a practical treatment plan that should also include behavioral approaches as mindfulness-based cognitive therapy / acceptance and commitment training.

Leica Impact One™ Stereotaxic
CCI Instrument (Buffalo Grove, IL)



TBI coordinates for CCI device:

X= 3.0 mm (lateral to Bregma)

Y= -2.0 mm (posterior to Bregma)

Z= -1.5 mm (depth)

Impactor size (tip)= 5 mm

Probe velocity= 4 m/s

Probe angle= 15°

Dwell time= 100 ms

No craniotomy (closed head injury)

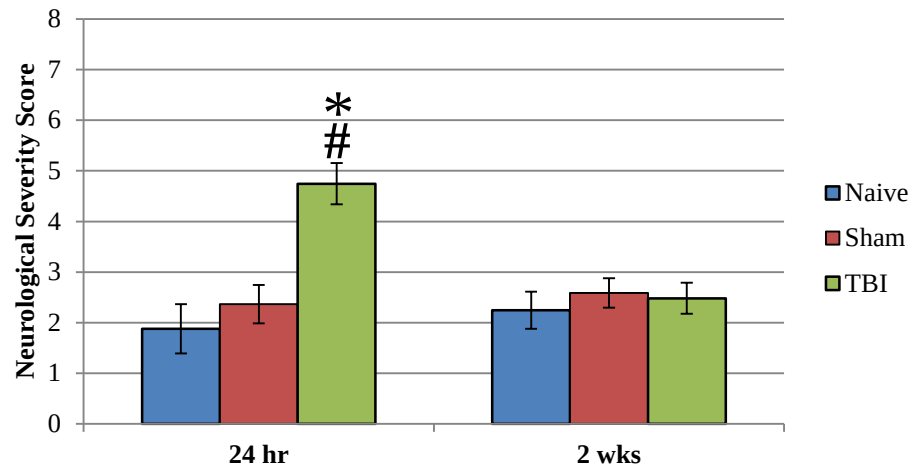
1x TBI or 3x TBI (every 24h)

Figure 1: Model of repetitive TBI closed head injury.

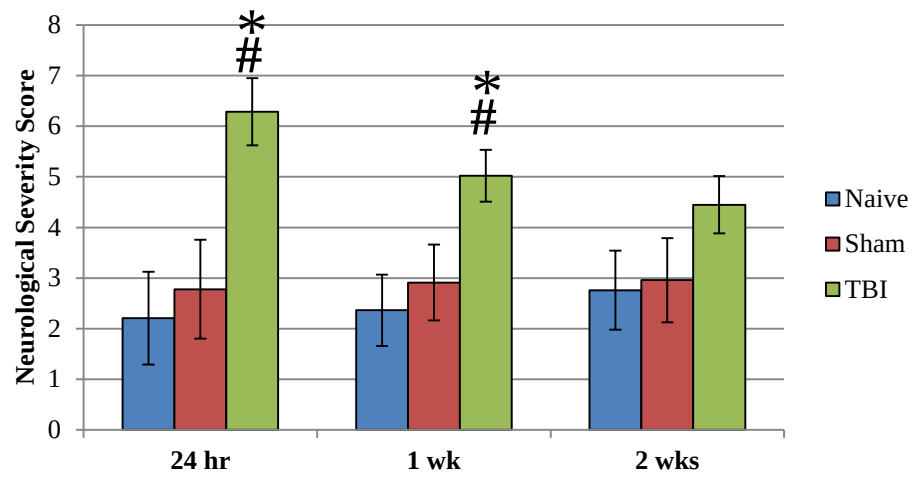
The coordinates of the impactor, velocity and its size are specified in the figure. Mice were placed in stereotaxic frame with eye lubricant to protect the cornea during surgery. The electromagnetically controlled impactor directly struck the exposed cranium superior to the left hemisphere over the parietal cortex. In the sham control group, all surgical procedures were performed with the exception of the impactor application. Therefore, the left hippocampus was ipsilateral to the injury site, whereas the right hemisphere was contralateral to the injury site. The injury protocol was approved by USUHS IAUC. After impact, the skin was sutured. Mice recovered from anesthesia on a warming pad and then were placed in their home cages. The handling of the mice and duration of anesthesia were the same for TBI and sham injured mice to minimize confounding factors related to repetitive use of anesthesia and mouse handling.

A.

mNSS-R: 1X CHI



mNSS-R: 3X CHI

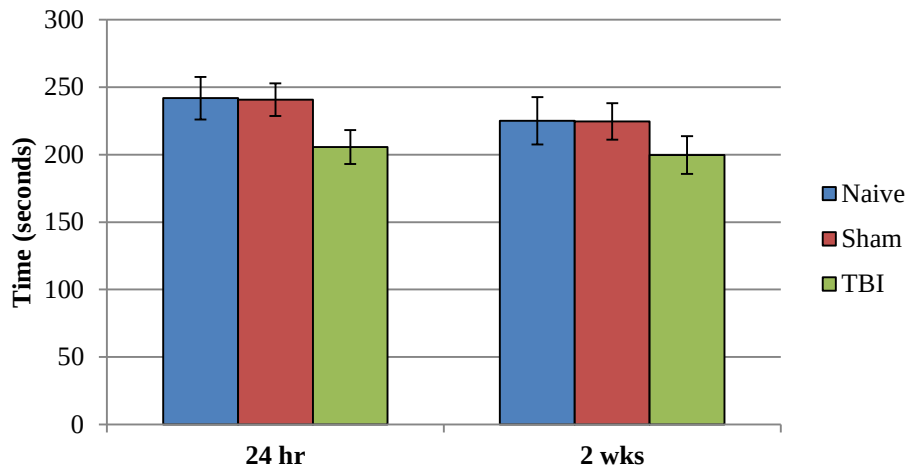


* - CHI significantly different from Naïve ($p < .005$)

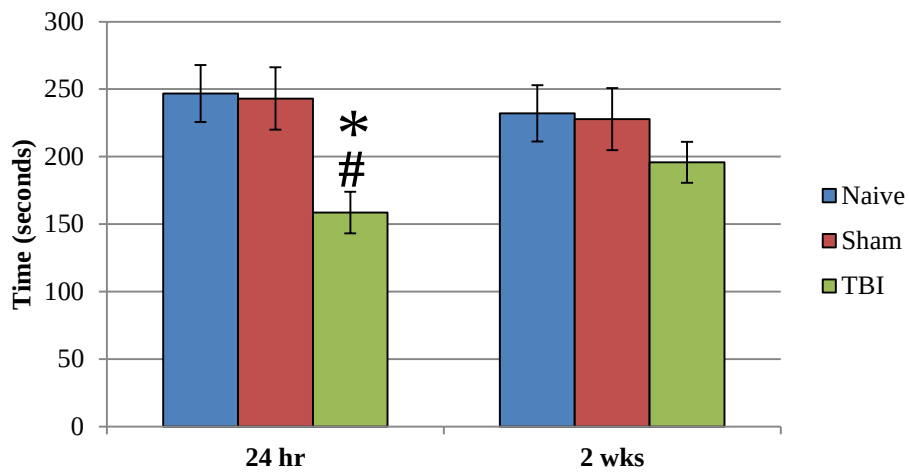
- CHI significantly different from Sham ($p < .005$)

B.

Rotarod Performance: 1X CHI



Rotarod Performance: 3X CHI

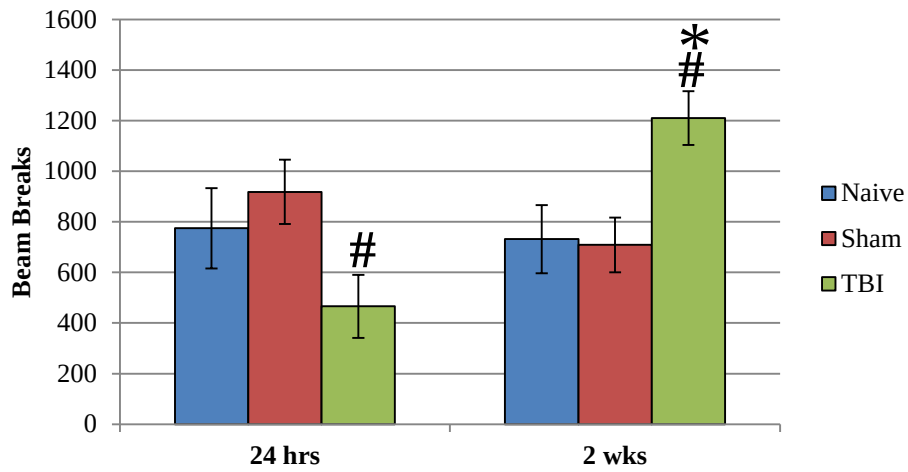


* - TBI significantly different from Naïve ($p=.001$)

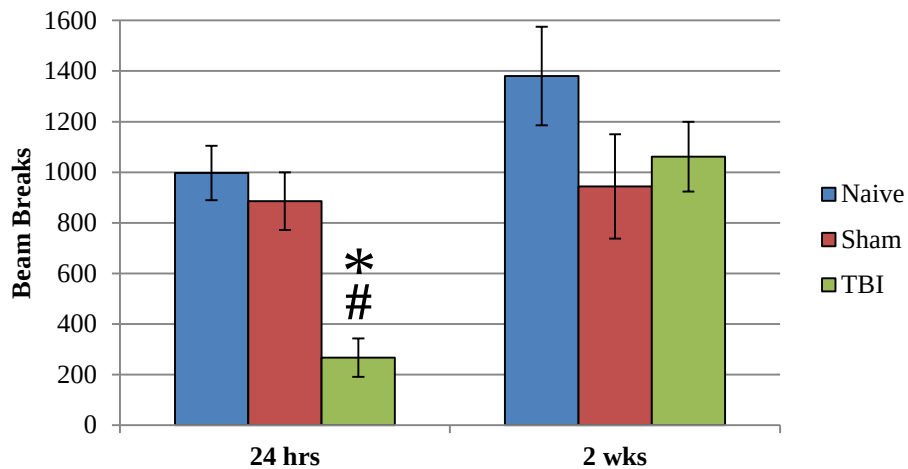
- TBI significantly different from Sham ($p=.001$)

C.

Vertical Activity: 1X CHI



Vertical Activity: 3X CHI



* - TBI significantly different from Naïve ($p=.001$)

- TBI significantly different from Sham ($p=.001$)

Figure 2: 3X CHI impacted outcome of behavioral tests between 24 hours and one week following injury. (A)

Abnormal Mouse Neurological Severity Scale – Revised (mNSS-R) score revealed time dependent changes in mNSS-R indicating underlying changes in motor and sensory reflexes. Tests included: balance, landing response, tail raise, drag, righting, ear reflex, eye reflex, sound reflex, tail pinch, and foot pinch and was scored by observers blinded to injury as follow: 0 = normal response; 1 = partial and/or compromised response; 2 = no response. 3X CHI significantly differed from Naïve ($p<0.005$). 3X CHI significantly different from Sham ($p<0.005$). **(B)** Rotarod performance was significantly impacted by 3X CHI at 24 hours. 3X CHI was significantly different from Naïve ($p<0.01$), 3X CHI significantly differed from Sham ($p<0.01$). **(C)** Open field vertical activity was impacted by 3X CHI and 1X CHI at 24 hours following injury. Increase in vertical activity in 1X CHI at the 2-week time point may be explained by increase in anxiety in this group of mice (e.g. stress related). 3X CHI was significantly different from Naïve ($p<0.01$), 3X CHI was significantly different from Sham ($p<0.01$). Mouse groups: 1X CHI (11 naïve, 12 Sham, and 16 TBI) and 3xTBI (12 naïve, 1Sham, 22 TBI) (Experiments were performed by members of Dr. Grunberg laboratory, and Dr. Ranjana Verma of the Galdzicki laboratory).

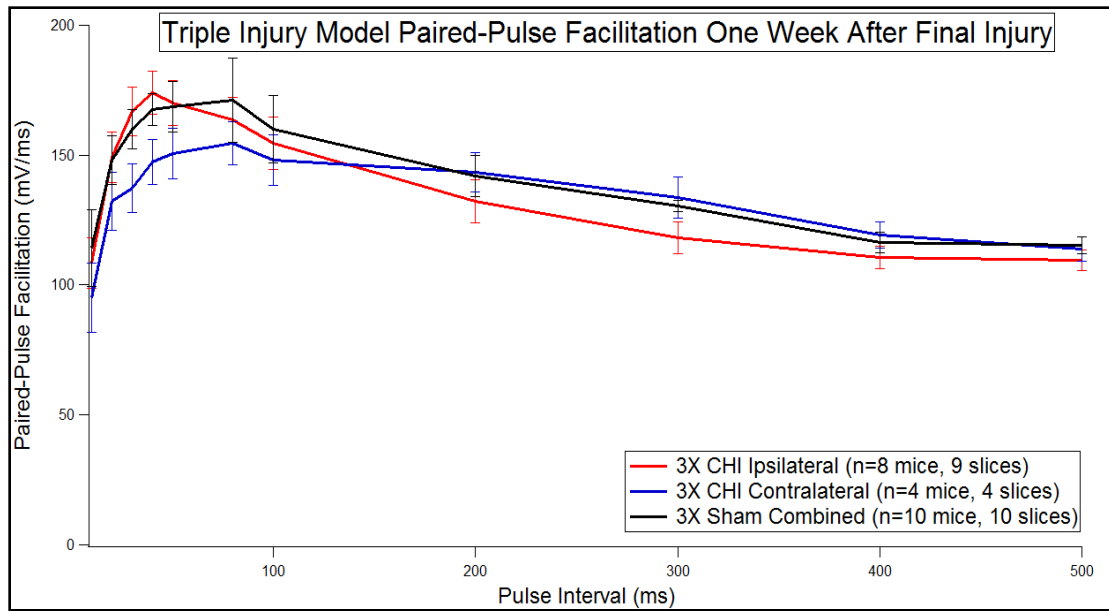


Figure 3: Schaffer collateral-CA1 synapses exhibit normal paired-pulse facilitation in 3X CHI mice one week after the final injury.

Using a constant stimulus intensity (mA) that evokes 30% of the maximal fEPSP response, a 30-minute baseline was acquired. For each pulse interval (ms), a single value was acquired by averaging five consecutive waveforms that were obtained by applying a single stimulus of constant intensity (mA) every 60 s. The pulse intervals (ms) used were: 500, 400, 300, 200, 100, 80, 50, 40, 30, 20, and 10. Facilitation was observed to begin at approximately the 300 ms stimulus interval, and persist to the 80 ms stimulus interval. Stimulus intervals less than 80 ms produced a depression, when comparing the percent change slope (mV/ms) of the second response to the first response. Statistical analysis was performed with repeated measures ANOVA ($p < 0.05$).

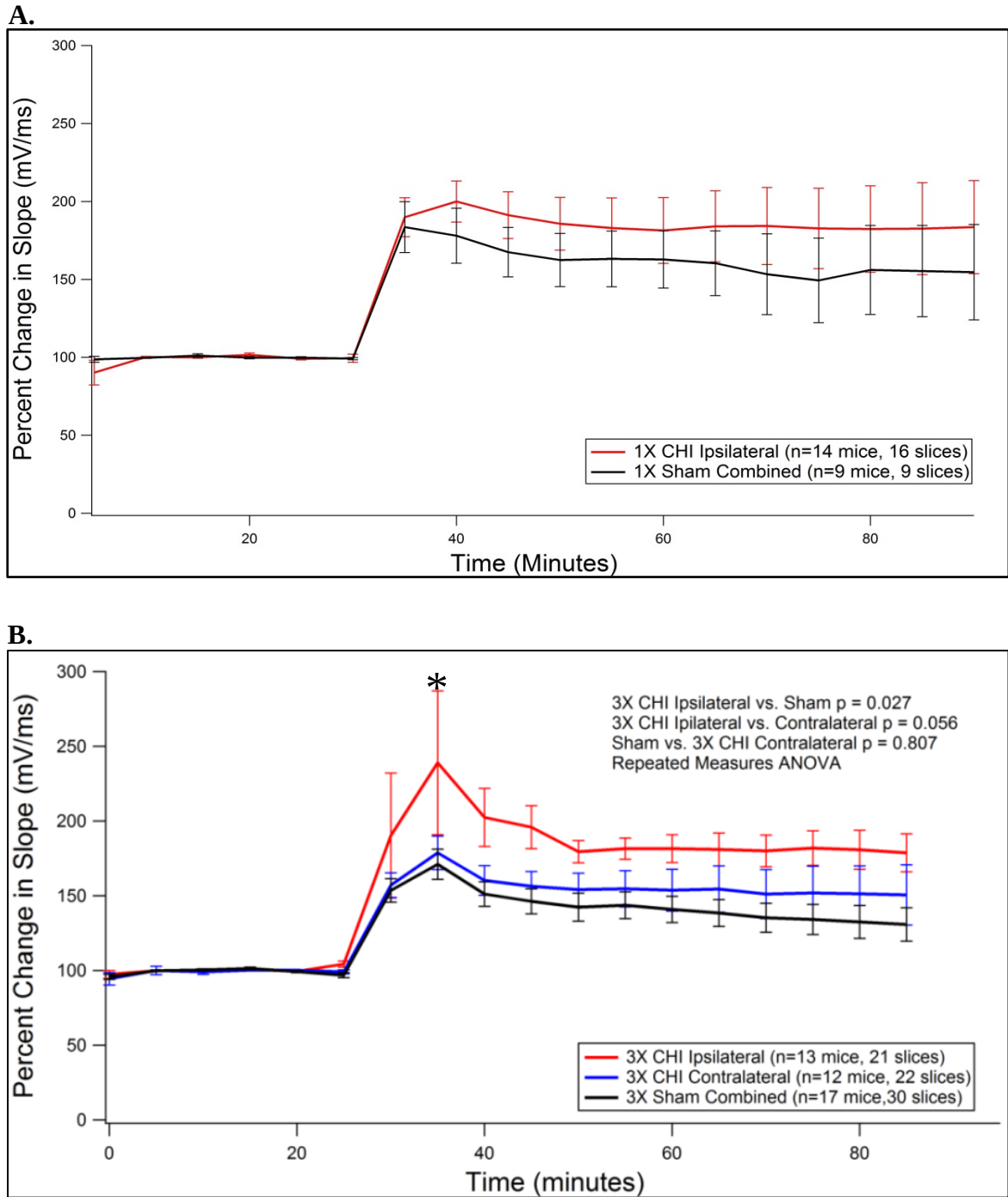


Figure 4: Enhanced CA1 hippocampal long-term potentiation observed in 3X CHI mice one week after the final injury. (A)

Normal CA1 hippocampal long-term potentiation observed in 1X CHI mice one week after the final injury. **(B)** Augmented CA1 hippocampal long-term potentiation observed in 3X CHI mice one week after the final injury. Extracellular field potential recordings of 400 μ m hippocampal slices were conducted one week after the third and final injury to

observe changes in long-term potentiation (LTP). Positioned in the Schaffer collaterals, the stimulating electrode delivered a single stimulus every 60 seconds for 30 minutes to establish a baseline. At 30 minutes, tetanus was applied (100 Hz for 1 second) to evoke LTP in the stratum radiatum of field CA1. Recordings continued for 60 minutes after tetanus. 3X CHI ipsilateral slices had an increased percent slope change with respect to those from sham-injured mice. Statistical analysis was performed using repeated measures ANOVA ($p < 0.05$).

	V_m (mV)		C_m (M Ω)		R_m (M Ω)		Tau (ms)	
	3X CHI	3X Sham	3X CHI	3X Sham	3X CHI	3X Sham	3X CHI	3X Sham
N	65 cells from 14 mice	39 cells from 10 mice	65 cells from 14 mice	39 cells from 10 mice	65 cells from 14 mice	39 cells from 10 mice	65 cells from 14 mice	39 cells from 10 mice
Mean	-57.3	-57.6	121.4	118.0	69.1	74.8	5.0	5.0
SEM	1.0	1.4	5.6	6.0	6.6	9.3	0.0	0.0
P- value	0.413		0.342		0.310		0.230	

Table 1: Passive intrinsic membrane properties are unaffected by 3X CHI, one week after the final injury.

A 5mV hyperpolarizing step from a holding potential of -70 mV was applied to estimate the membrane capacitance (C_m in pF) and membrane resistance (R_m in M Ω) at the initiation of the whole-cell access and at intervals throughout the recording. Likewise, the resting membrane potential (V_m in mV) was measured in current-clamp ($I=0$ mode) at the beginning of each recording, and throughout the experiment to assess and monitor cell viability. The membrane time constant, tau, was calculated by multiplying the value of the membrane capacitance by the membrane resistance. Recordings were performed in voltage-clamp configuration. Statistical analysis was performed using a Student's t-test ($p < 0.05$).

	Rheobase (pA)		Threshold (mV)		Threshold to Afterhyperpolarization (mV)		Afterhyperpolarization Minimum (mV)	
	3X CHI	3X Sham	3X CHI	3X Sham	3X CHI	3X Sham	3X CHI	3X Sham
N	65 cells from 14 mice	39 cells from 10 mice	65 cells from 14 mice	39 cells from 10 mice	65 cells from 14 mice	39 cells from 10 mice	65 cells from 14 mice	39 cells from 10 mice
Mean	14.3	15.1	-47.1	-46.8	9.46	9.67	-56.5	-57.1
SEM	0.74	1.02	4.94	1.05	1.09	1.61	0.89	1.78
P-value	0.26		0.41		0.46		0.40	

Table 2: Four of the active intrinsic membrane properties are unaffected by 3X CHI, one week after the final injury.

Action potentials were elicited from regular-spiking neurons in area CA1 at increasing steps (20 pA) while recording in I-Clamp Normal mode at -70 mV with pClamp analytical software. Spike threshold was evaluated by visually identifying the voltage at which maximum acceleration occurred within the rising phase of the first spike of the neuron. We generally observed that the first action potential in these neurons exhibited multiple spikes (ranging from 2-10 spikes). The IGOR analysis program, written in house, analyzed the first spike. Properties featured in Table 2 are rheobase (pA), threshold (mV), threshold to afterhyperpolarization (mV), and after-hyperpolarization minimum (mV). Statistical analysis was performed using a Student's t-test ($p < 0.05$).

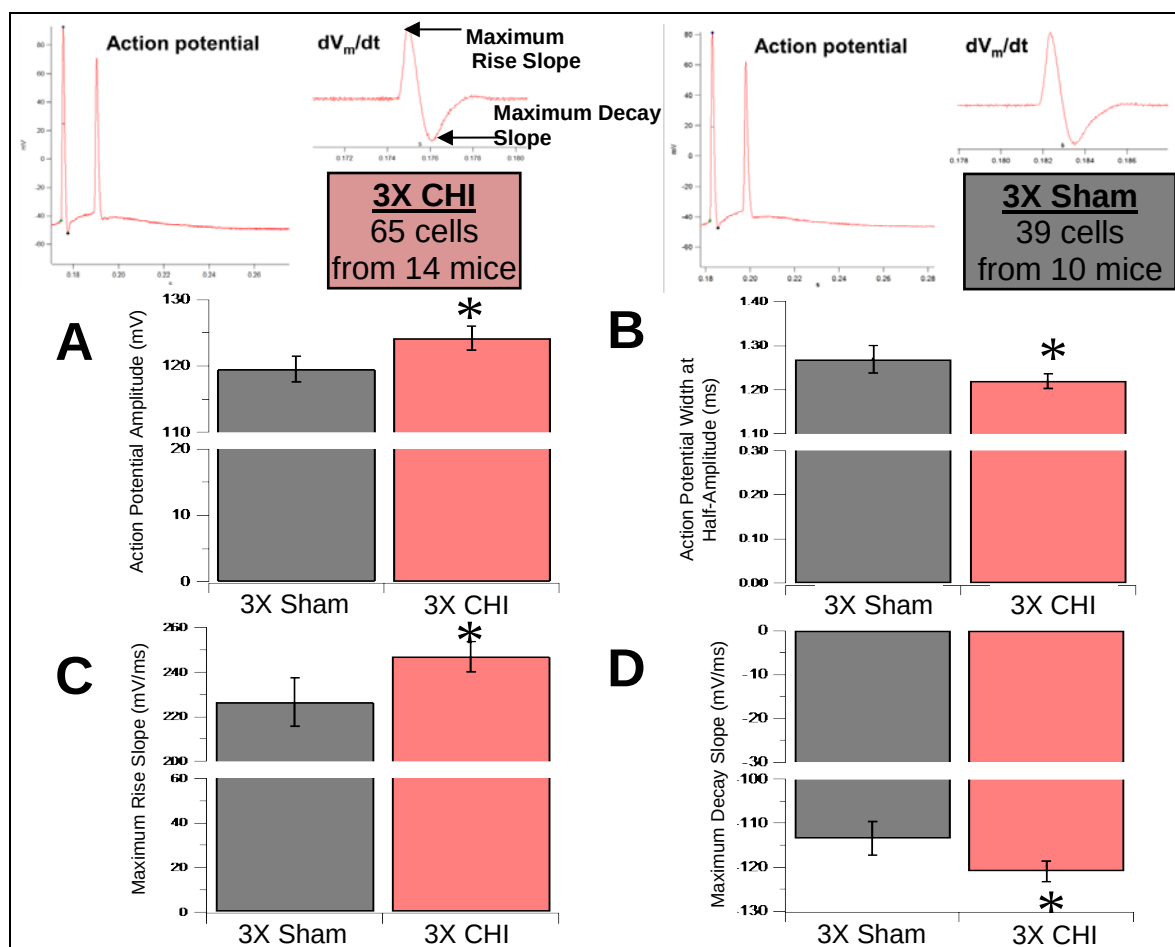


Figure 5: Active intrinsic properties of CA1 hippocampal pyramidal neurons are altered by 3X CHI one week after the final injury.

In the presence of potassium-gluconate intracellular solution, CA1 pyramidal neurons were whole-cell patch clamped. Recordings were conducted in current-clamp normal (I-normal), with the holding potential set at -70 mV. 20 pA of current were applied per sweep, for a total of ten sweeps. The first action potential fired with the minimum amount of required current was then analyzed using an IGOR program written in house. Representative traces for both 3X CHI (top left) and 3X Sham (top right) demonstrate the firing pattern of the first action potential fired by the CA1 pyramidal neurons. Significant changes were observed in action potential amplitude (mV) (A), action potential width at half-amplitude (ms) (B), maximum rise slope (mV/ms) (C), and maximum decay slope (mV/ms) (D). 3X CHI (n) = 65 cells from 14 mice, and 3X Sham (n) = 39 cells from 10 mice. Statistical analysis was performed by Student's t-test (p < 0.05).

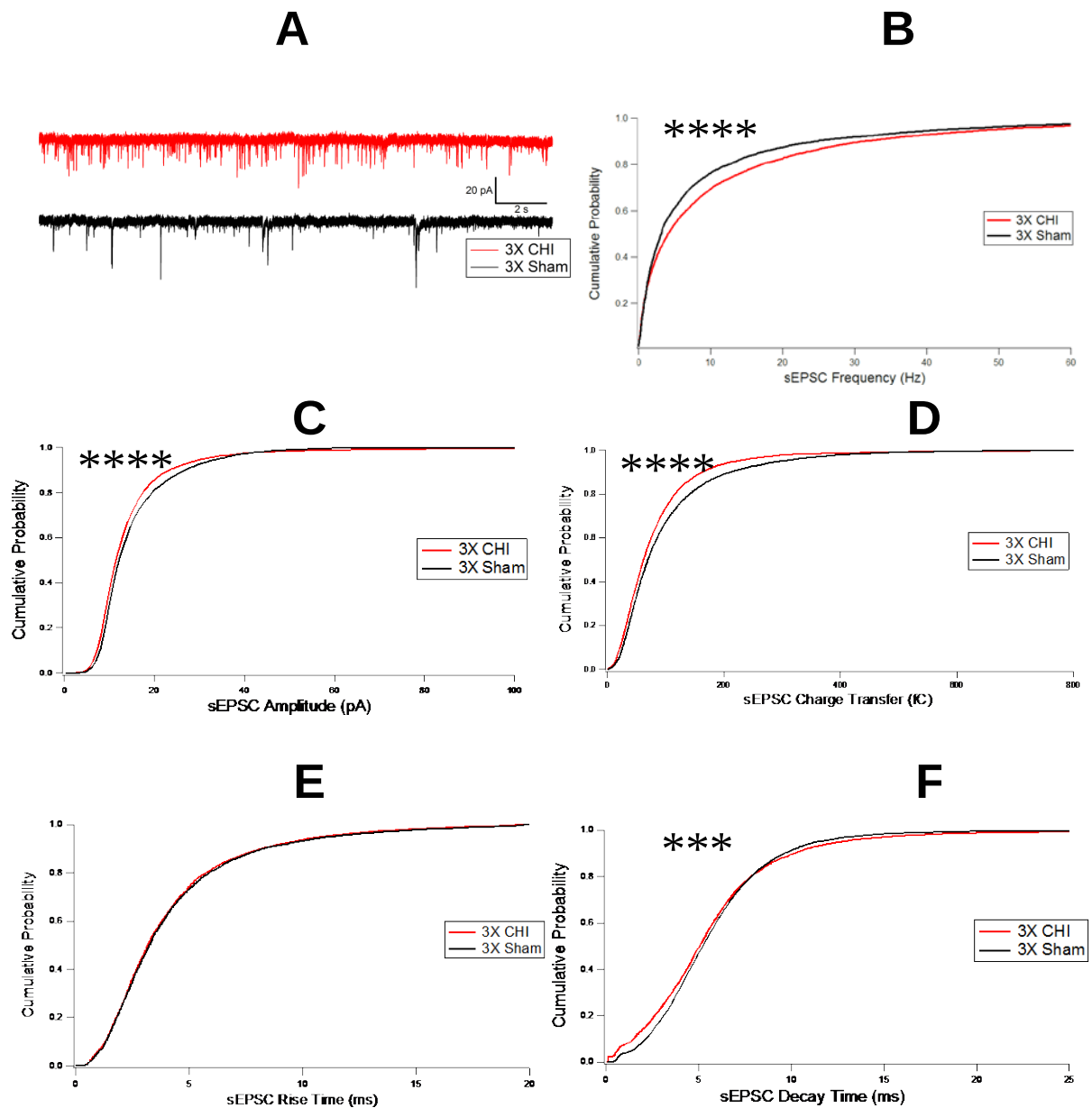


Figure 6: 3X CHI alters spontaneous excitatory postsynaptic currents (sEPSCs) of CA1 hippocampal pyramidal neurons one week after the final injury. (A) Representative traces show increased frequency of events for the 3X CHI cells, while the 3X Sham cells exhibit a larger peak amplitude. Cumulative probability plots show that the 3X CHI cells demonstrate increased sEPSC frequency (B), decreased peak amplitude (C), decreased charge transfer (D), not significantly altered maximum rise time (E), and significantly altered maximum decay time (F). For the 3X CHI group, 25 cells were recorded from a total of 6 mice. For the 3X Sham group, 20 cells were recorded from 5 mice. Statistical analysis was performed using the Kolmogorov-Smirnov test with IGOR analytical software. The symbol **** indicates a significant difference from 3X Sham ($p < 0.0001$). The symbol *** indicates a significant difference from 3X Sham ($p < 0.001$).

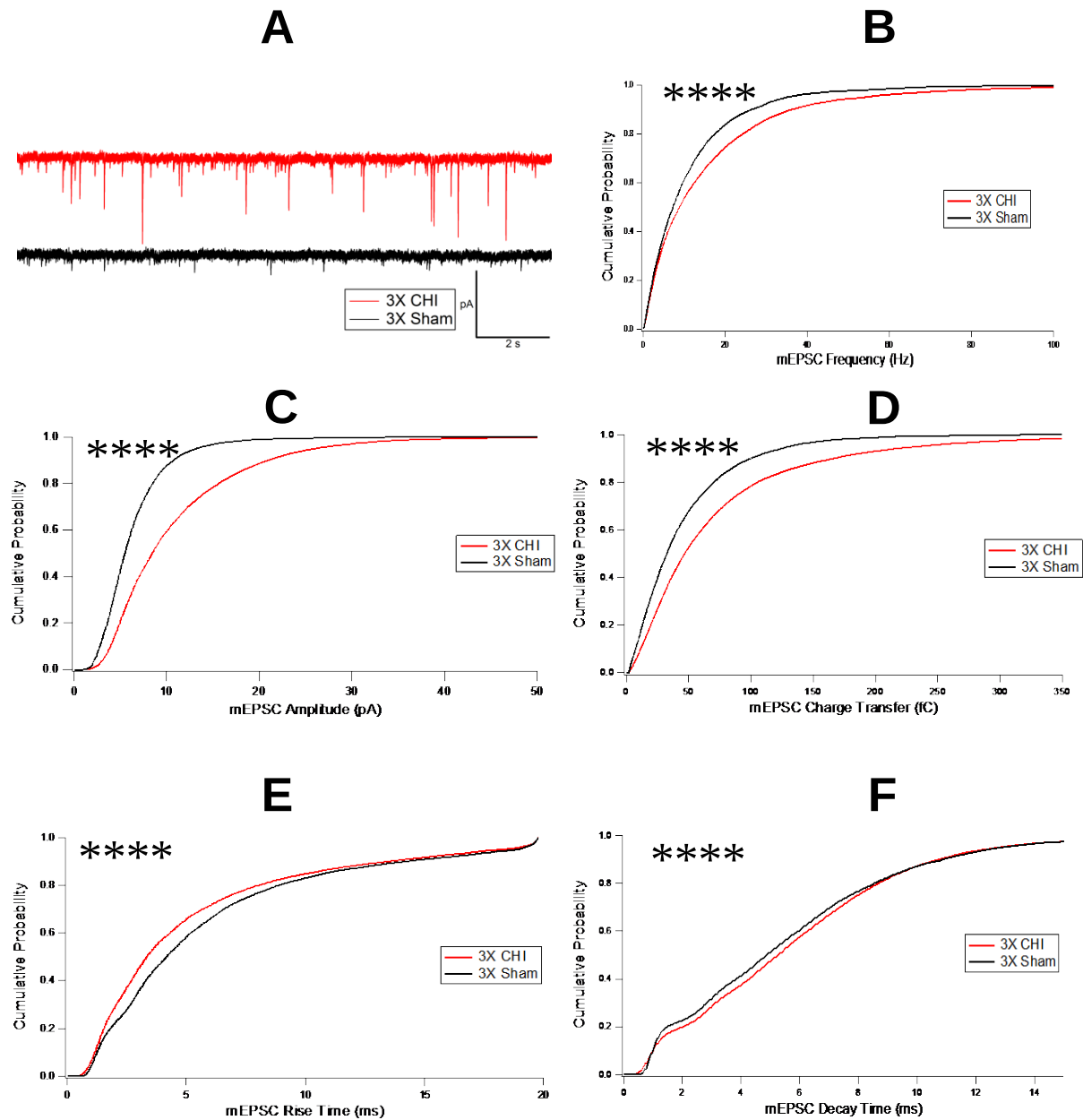


Figure 7: 3X CHI alters miniature excitatory postsynaptic currents (mEPSCs) of CA1 hippocampal pyramidal neurons one week after the final injury.

1 μ M tetrodotoxin (TTX) was added to the ACSF to block voltage-gated sodium channel activity. (A) Representative traces show increased both frequency of mEPSCs and larger peak amplitude for the 3X CHI cells. Cumulative probability plots show that the 3X CHI cells demonstrate increased sIPSC frequency (B), increased peak amplitude (C), increased charge transfer (D), decreased maximum rise time (E), and increased maximum decay time (F). For the 3X CHI group, 25 cells were recorded from a total of 6 mice. For the 3X Sham group, 20 cells were recorded from 5 mice. Statistical analysis was performed using the Kolmogorov-Smirnov test with IGOR analytical software. The symbol **** indicates a significant difference from 3X Sham ($p < 0.0001$).

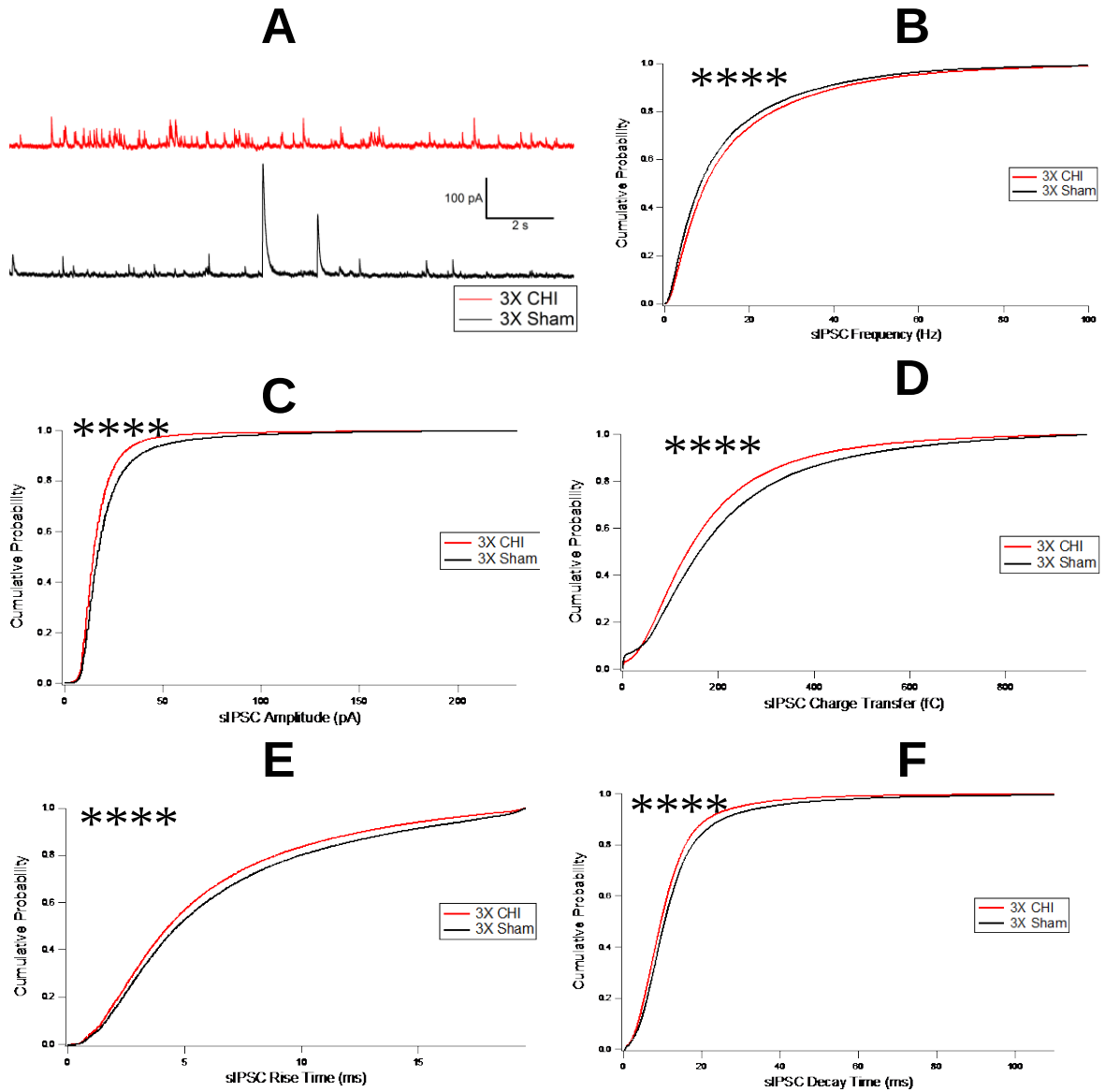


Figure 8: 3X CHI alters spontaneous inhibitory postsynaptic currents (sIPSCs) of CA1 hippocampal pyramidal neurons one week after the final injury.

3X CHI alters spontaneous inhibitory postsynaptic currents (sIPSCs) one week after the final injury. Representative traces show increased frequency of events for the 3X CHI cells, while the 3X Sham cells exhibit a larger peak amplitude (A). Cumulative probability plots show that the 3X CHI cells demonstrate (B). increased sIPSC frequency, decreased peak amplitude (C), decreased charge transfer (D), decreased maximum rise time (E), and decreased maximum decay time (F). For the 3X CHI group, 25 cells were recorded from a total of 6 mice. For the 3X Sham group, 20 cells were recorded from 5 mice. Statistical analysis was performed using the Kolmogorov-Smirnov test with IGOR analytical software. The symbol **** indicates a significant difference from 3X Sham ($p < 0.0001$).

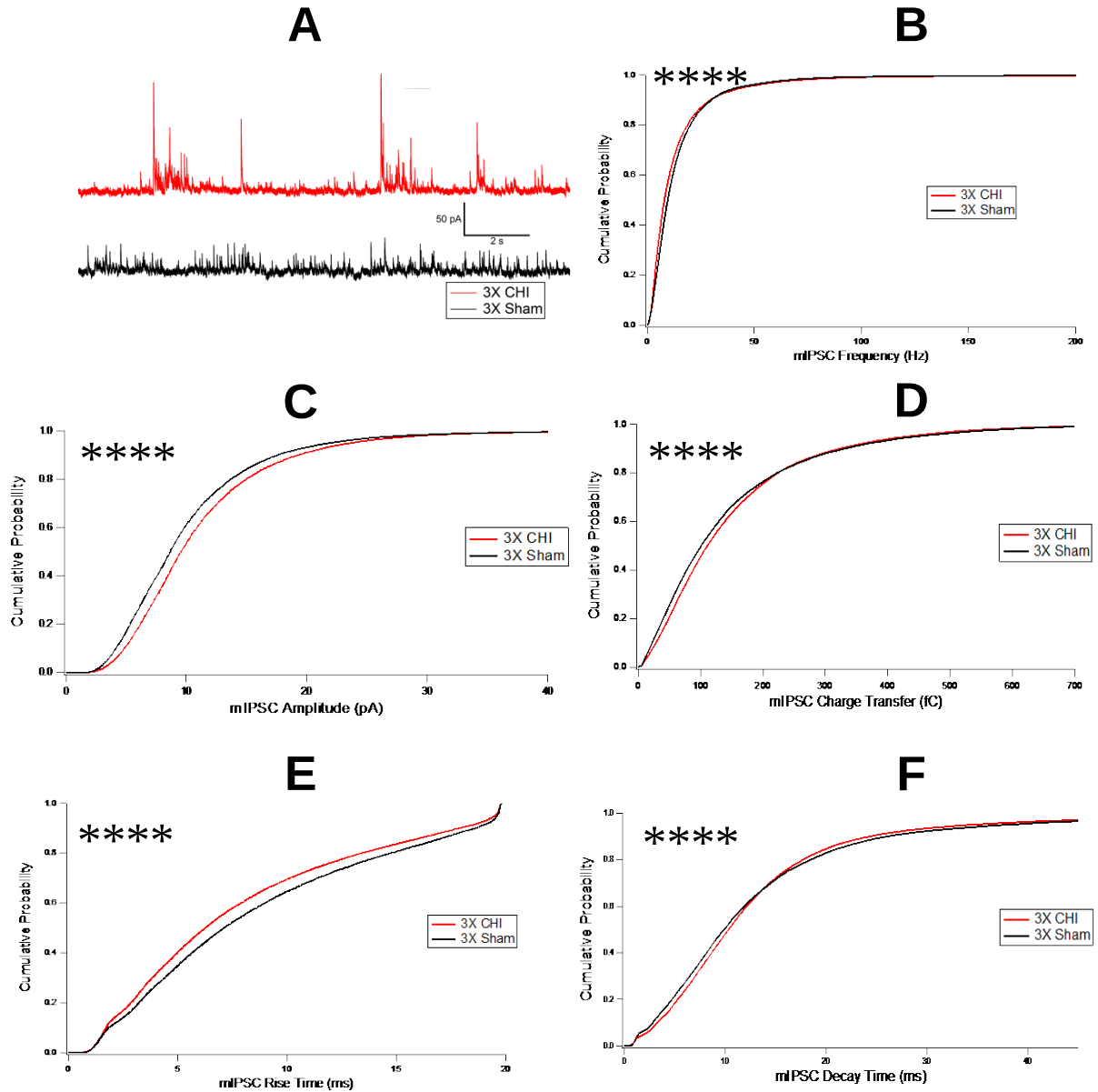


Figure 9: 3X CHI alters miniature inhibitory postsynaptic currents (mIPSCs) of CA1 hippocampal pyramidal neurons one week after the final injury.

1 μ M tetrodotoxin (TTX) was added to the ACSF to block voltage-gated sodium channel activity. Representative traces show a larger peak amplitude for the 3X CHI cells, while the 3X Sham cells exhibit an increased frequency of mIPSCs (A). Cumulative probability plots show that the 3X CHI cells demonstrate decreased sIPSC frequency (B), increased peak amplitude (C), increased charge transfer (D), decreased maximum rise time (E), and increased maximum decay time (F). For the 3X CHI group, 25 cells were recorded from a total of 6 mice. For the 3X Sham group, 20 cells were recorded from 5 mice. Statistical analysis was performed using the Kolmogorov-Smirnov test with IGOR analytical software. The symbol **** indicates a significant difference from 3X Sham ($p < 0.0001$).

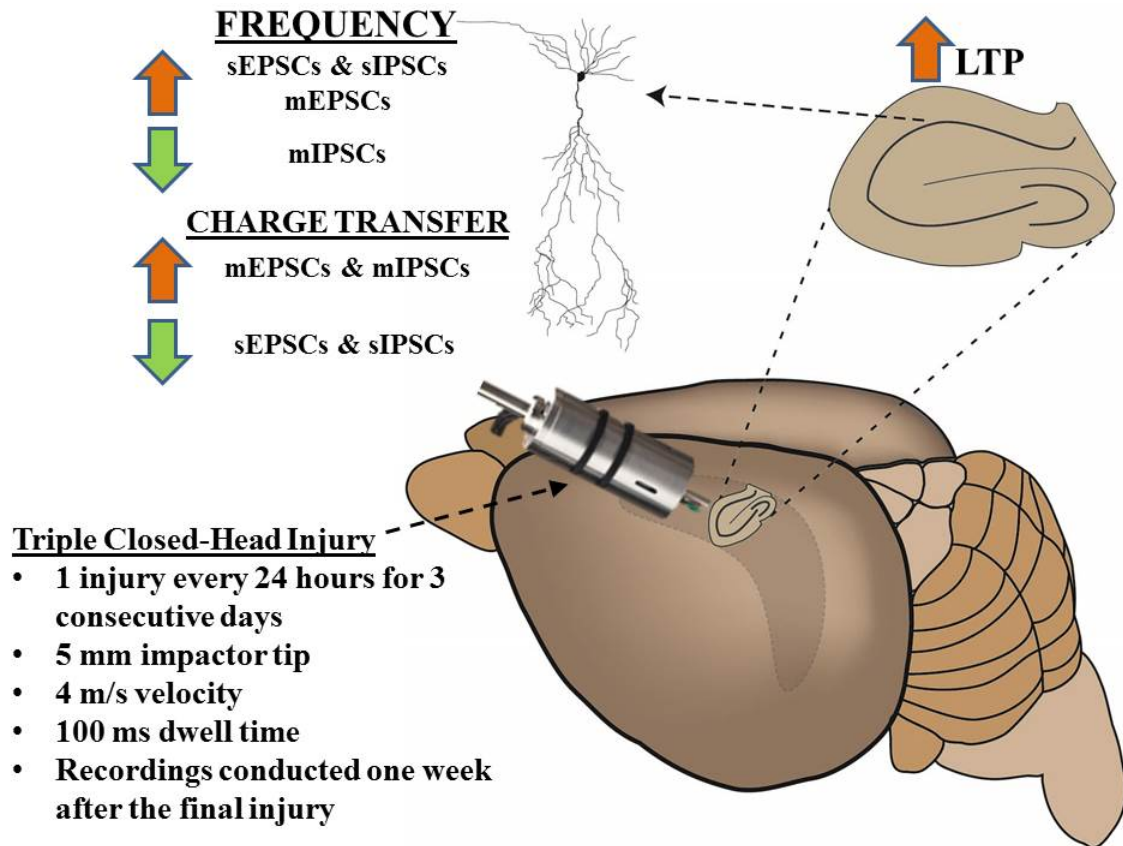
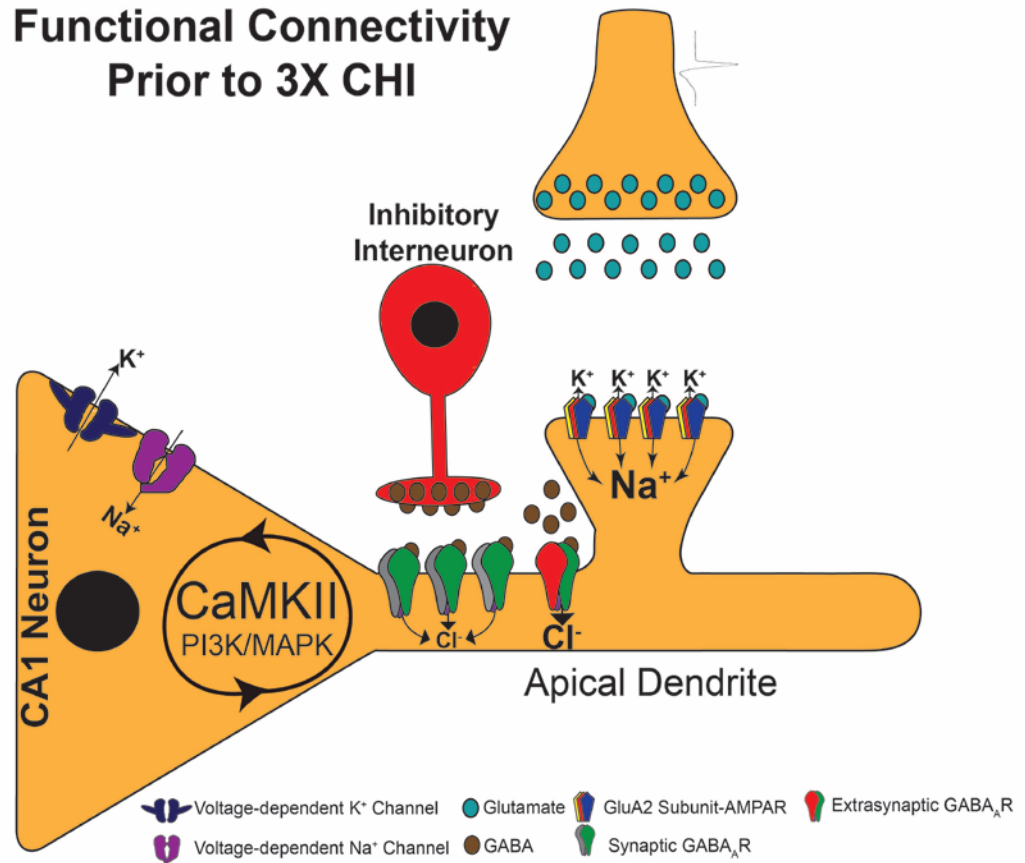


Figure 10: 3X CHI causes a shift between excitatory and inhibitory inputs to CA1 pyramidal neurons and changes to their intrinsic active properties.

As illustrated above, extracellular field potential recordings revealed enhanced LTP in hippocampal slices that ipsilateral to the injury. Whole-cell patch-clamp recordings demonstrated significant changes to the active intrinsic membrane properties that include increased action potential amplitude, decreased action potential width, and increased both rise slope and decay slope of action potential. Voltage-clamp recordings exhibited increased frequencies of events for spontaneous excitatory postsynaptic currents, spontaneous inhibitory postsynaptic currents, as well as action-potential-independent miniature excitatory postsynaptic currents. However, the miniature inhibitory postsynaptic currents had a decreased frequency of events. Both the miniature excitatory and miniature inhibitory postsynaptic currents demonstrated increases in charge transfer. Conversely, the action potential-dependent spontaneous excitatory and inhibitory postsynaptic currents experienced decreases in charge transfer.

A.

Functional Connectivity Prior to 3X CHI



B.

Functional Alterations After 3X CHI

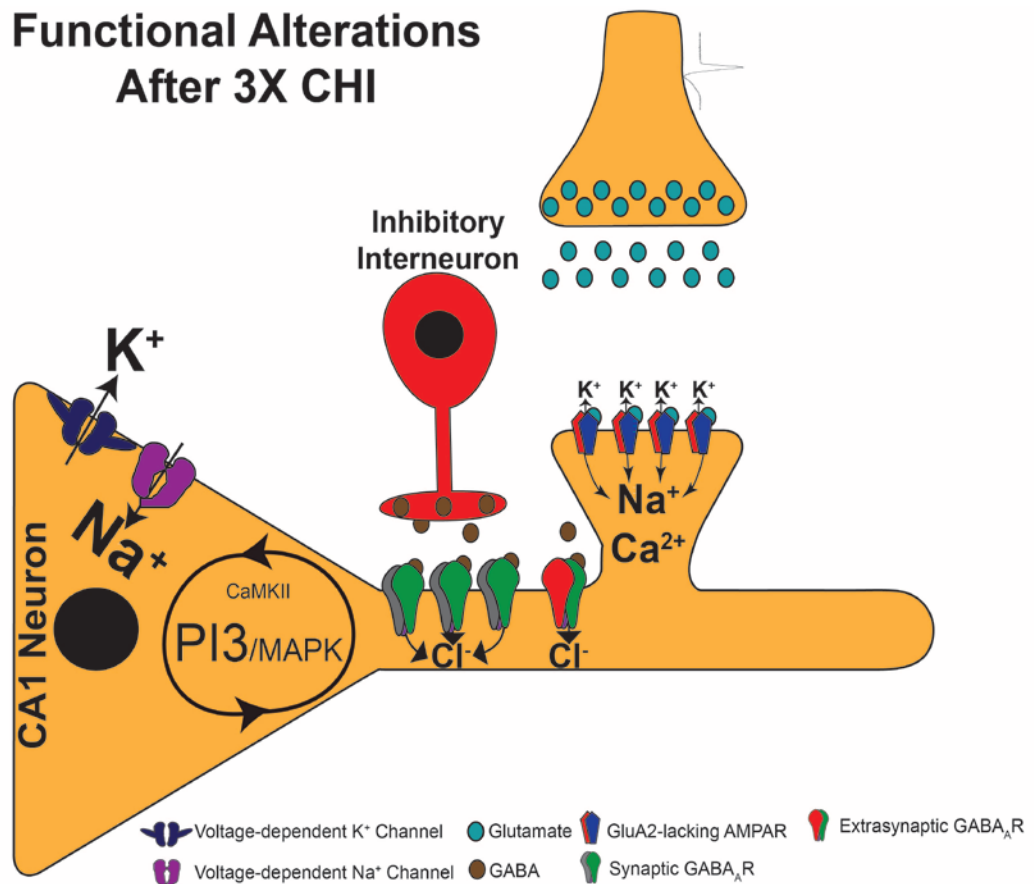


Figure 11: Summary of electrophysiological changes in CA1 hippocampal pyramidal neurons resulting from 3X CHI.

This diagram depicts the results of electrophysiological experiments and is consistent with impact of 3X CHI on the electrophysiological properties of CA1 pyramidal neurons by the differential regulation of the subunits that comprise excitatory AMPA and inhibitory GABA_A receptors, and voltage-dependent sodium and potassium channels. Posttranslational modifications of synaptic AMPARs, GABARs and voltage-dependent sodium and potassium channels leading to their higher conductance would also support presented results. **(A)** Before the triple injury, excitatory synapses are mostly comprised of AMPARs containing GluA2 receptors that make these receptors non-permeable to Ca²⁺; **(B)** Following 3XCHI, excitatory synapses become stronger, and we hypothesize that this could be consistent with AMPARs lacking the GluA2 subunit that make them permeable for Ca²⁺. Following 3XCHI inhibitory synapses become stronger as well, and similarly this can suggest the insertion of GABA receptors with a higher Cl⁻ conductance at the inhibitory synapses. In addition, changes in intrinsic active properties are consistent with increased voltage-dependent sodium and potassium currents following injury.

Proposed Mechanism:
Differential Subunit
Regulation by TNF α

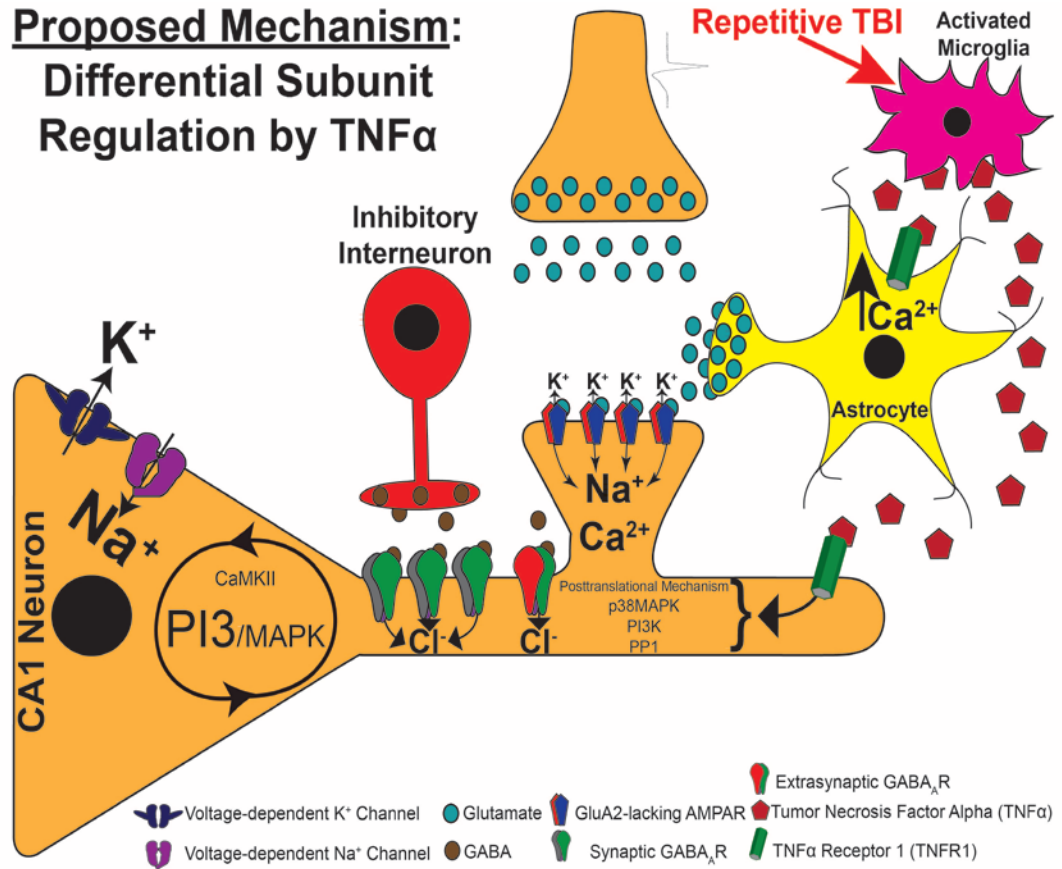


Figure 12: Proposed mechanism for the neuroinflammatory-mediated differential subunit regulation of excitatory AMPA and inhibitory GABA_A receptors, and voltage dependent sodium and potassium currents that resulted from 3X CHI.

The changes proposed here would be consistent with augmented CA1 LTP in GluA2-lacking AMPAR synapses and a shift in signaling pathways that could explain changes in cognitive tests revealing impaired hippocampal function.

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