



National Institute of
Neurological Disorders
and Stroke

WORKSHOP SUMMARY

UNDERSTANDING TRAUMATIC BRAIN INJURY IN WOMEN

NIH Main Campus, December 18-19, 2017

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Executive Summary

Background

Approximately 2.8 million TBI-related emergency department visits, hospitalizations, and deaths occurred in the U.S. in 2013. TBI can have long-term sequelae including cognitive and physical disability, post-concussion syndrome, and possible contribution to the development of chronic traumatic encephalopathy. Some types of TBI have also been associated with chronic pain and can be comorbid with PTSD and depression. For many individuals, their caretakers, and families, TBI can be a life-changing event.

Unfortunately, many questions remain unanswered regarding the best treatments for TBI, how to translate preclinical findings into humans, and how TBI differs in women and men. The December 2017 workshop *Understanding Traumatic Brain Injury in Women* at the National Institutes of Health (NIH) convened investigators from many disciplines for a two-day meeting to address these and other questions in an effort to help better diagnose and treat women and men with TBI in the future.

Overview

Exploring sex differences in TBI has been difficult in the past because women have historically been under-represented in TBI clinical trials. In addition, preclinical studies have often excluded females or have used ovariectomized rather than intact animals, leading to an incomplete understanding of TBI in females.

This workshop focused on the existing knowledge regarding sex differences in TBI and how these differences can be incorporated into preclinical and clinical efforts moving forward. The workshop addressed the state of the science and identified both gaps and future directions for TBI research.

The event was convened as a joint effort between the National Institute of Neurological Disorders and Stroke (NINDS) and the NIH Office of Research on Women's Health. NINDS is the lead institute for TBI research. It supports TBI research through grants to major medical institutions across the country and conducts TBI research in its intramural laboratories and the Clinical Center at NIH.

This two-day workshop was divided into the following seven sessions: 1) Sex Differences in TBI across the Lifespan, 2) TBI as a Consequence of Intimate Partner Violence, 3) Sex Differences in Preclinical and Clinical Research, 4) Sex Differences following Sports-Related TBI, 5) Sex Differences in TBI among Service Members and Veterans, 6) Sex Differences in Diagnosis, Prognosis, and Management of TBI, and 7) Prioritization of Research Needs.

Common Themes

Some common themes resonated across presentations. The statements below were echoed by more than one researcher, sometimes from different fields. Common workshop themes included the following:

- Women have historically been underrepresented (or completely excluded) in many TBI studies.
- When women have been included, they made up a small proportion of study participants.

- In studies involving both women and men, data were not always stratified by sex making it difficult to ascertain sex differences.
- In some fields—such as TBI due to Intimate Partner Violence and pediatric TBI—there is a dearth of data and studies in the literature.

Key Findings

Key workshop findings included the following:

- Although more data and studies are needed, it is clear from the studies presented at the workshop that sex differences in TBI exist and can influence outcomes.
- Some fields of TBI research, such as sports- and military-related TBI, are further along than others in part due to increased funding and public interest in such areas.
- Partner-abused women are a unique group of TBI sufferers because of repetitive injuries over time and strangulation. However, no national TBI prevalence estimates exist and there is a dearth of research funding dedicated to this area.
- In the preclinical arena, there is a need for larger, multi-center trials to enhance reproducibility and comparison of results. There is also a need to develop biomarkers that can help translation from animal models into humans.
- Unfortunately, phase III clinical trials have not yielded favorable results. This could potentially be addressed by conducting larger phase II and smaller phase III trials.
- In future clinical trials, researchers should better select trial patients (e.g., type and grade of TBI), and take into account the patient's hormonal status at time of injury.
- Clinical neuroimaging can be useful in TBI research, but there is a need for standardization of assessment methods and analysis as different research groups are using different approaches, making it difficult to derive conclusions based on the data.
- For sports-related TBI, there is little or no national data on younger athletes, recreational sports, or traditionally understudied populations (e.g., rural, low SES, transgender athletes, etc.).
- Despite increasing involvement of women in the military and in combat roles, many military studies include only a very small proportion of females or exclude females altogether.
- Rehabilitation guidelines are needed to specify physical therapy and occupational therapy dosing in rehabilitation for TBI patients.
- Researchers should consider adapting models used in other fields, such as those in Alzheimer's disease or stroke, to TBI in order to examine the impact of sex on the performance of biomarkers, as well as other potential effects such as epigenetics, protein expression, etc.
- There is a significant amount of variability in TBI pediatric treatments. Although this may be partially addressed by the ADAPT trial, future pediatric trials should control for GCS scores as mortality can vary significantly based on these scores.

At the end of the conference, researchers convened to identify research gaps and prioritize future research areas. This yielded numerous recommendations (see in Section VII).

Conclusion

Studies presented during the workshop clearly showed TBI sex differences in neuron anatomy, neural mechanisms, gonadal hormones, immunity response, and symptoms. These studies make a strong case for increased future research in the area of TBI sex differences, especially for preclinical and clinical studies involving a larger number of females.

Introduction

Through the workshop *Understanding Traumatic Brain Injury in Women*, a diverse group of investigators was convened at NIH to present some of the latest research related to Traumatic Brain Injury (TBI). The meeting's objectives were to present research on sex differences within the TBI field as well as to identify knowledge gaps and prioritize future research needs for TBI.

During the workshop, various TBI-related topics were presented and discussed including epidemiology, TBI and intimate partner violence, TBI among veterans, sports-related TBI, TBI biomarkers, preclinical studies, clinical trials, clinical management, and TBI in pediatric and adult populations. Most importantly, sex differences in TBI were also addressed as well as gaps and research priorities.

Background

It is estimated that TBIs contribute to about 30% of all injury deaths in the U.S.¹ In 2013, about 2.8 million TBI-related emergency department visits, hospitalizations, and deaths occurred in the U.S.¹ TBI can have long-term sequelae including cognitive and physical disability, post-concussion syndrome, and possible contribution to the development of chronic traumatic encephalopathy. Some types of TBI have also been associated with chronic pain and can be comorbid with PTSD and depression. For many individuals, their caretakers, and families, TBI can be a life-changing event.

In 2017, NIH allocated \$110 million to support work and research related to TBI. Within the NIH, the National Institute of Neurological Disorders and Stroke (NINDS) is the lead institute for TBI research. Like the injury, the NINDS portfolio is heterogeneous and spans a broad range of TBI scientific investigation including basic mechanistic, translational, and clinical research including all phases of clinical trials. NINDS also supports TBI research through grants to major medical institutions across the country and conducts TBI research in its intramural laboratories and the Clinical Center at NIH.

Over the years, research has expanded from a singular focus on severe TBI to finding better ways to diagnose, treat, and prevent all forms of TBI. Exploring sex differences in TBI has been difficult in part because women have historically been underrepresented in TBI clinical trials. In addition, preclinical studies have often excluded females or have used ovariectomized rather than intact animals, leading to an incomplete understanding of TBI in females.

This workshop focused on the existing knowledge regarding sex differences in TBI research and how these differences can be incorporated in preclinical and clinical efforts moving forward. More specifically, investigators with a wide swath of expertise addressed TBI by presenting on the following six broad sessions:

- Sex Differences in TBI across the Lifespan
- TBI as a Consequence of Intimate Partner Violence
- Sex Differences in Preclinical and Clinical Research
- Sex Differences following Sports-Related TBI

¹ Centers for Disease Control and Prevention. Accessed 1/20/2018.
www.cdc.gov/traumaticbraininjury/get_the_facts.html

- Sex Differences among Service Members
- Sex Differences in Diagnosis, Prognosis, and Management of TBI

Summaries of the presentations for each of these sessions are discussed below after the remarks provided by the director of NINDS and the Keynote presentation.

Welcome

Walter Koroshetz, MD, Director, National Institute of Neurological Disorders and Stroke (NINDS), NIH

Dr. Koroshetz said the mission of the National Institute of Neurological Disorders and Stroke is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. NINDS invests in basic, translational, and clinical research and works to identify both gaps in research and public health needs.

In 2016, NIH adopted a policy on sex as a biological variable. NIH expects sex as a biological variable to be factored into research designs, analyses, and reporting in vertebrate animal and human studies. By asking researchers to take sex into account when designing studies and evaluating results, NIH will ensure that the influence of sex is examined across the spectrum of biomedical research. Appropriate consideration of the influence of sex in basic, preclinical, and translational research will lead to a stronger foundation on which to build clinical research and trials.

NINDS funded more than 190 extramural TBI grants in 2016 alone. This investment spans a broad range of efforts from basic disease research to clinical trials. Topics funded include acute neuroprotection, neurorecovery, reduction of edema, controlling neuroinflammation, and understanding of the metabolic and neuroendocrine cascades.

These studies promise to provide answers to many outstanding questions that can help to better comprehend TBI sex differences, improve patient stratification, and provide a better understanding of the effectiveness of current clinical guidelines.

Keynote: Identifying Sex Differences in Research: What Are the Challenges?

Margaret McCarthy, PhD, University of Maryland School of Medicine

Dr. McCarthy explained that the brain is the first organ to form and the last to mature. While babies are typically born with functioning heart, lungs, and livers, the brain is still in its nascent stage at birth. This occurs so that the brain can begin to imprint the environment into its structure and function.

When Dr. McCarthy began her research career, it was believed that sex differences were mostly related to reproduction. Back then researchers believed the only sex differences in the brain were in areas directly associated with either reproductive behavior or physiology. However, in the past decades researchers have found that sex differences in the brain are widespread. For example, brain neurogenesis, glial genesis, and synaptogenesis all demonstrate sex differences.

It is important to keep in mind that gender is a human construct that embodies self and societal

perceptions of one's sex. Gender is fluid and can be expressed in a continuum. Sex, in contrast, is a biological construct that embodies chromosome complement and gonadal phenotype (i.e., XX vs. XY chromosomes). Thus, the study of sex differences involves studying the impact of *biological* sex in outcomes.

Incorporating sex as a clinical variable in research is important because the results from one sex can't always be generalized to the other. Also, some disorders of the nervous system show a sex bias with a higher prevalence of certain conditions in either males or females. For example, a male bias exists in ADHD, autism, dyslexia, and stuttering as these conditions are more commonly seen in males. In females, there is a higher prevalence of multiple sclerosis, PTSD, anxiety, and depression.

Despite these evident differences, there are various areas of neuroscience where studies have historically included few or no women. In addition, when both men and women are studied, the data are not always stratified by sex. Unfortunately, this also happens to be the case for TBI.

In the brain, sex differences are determined by genes, hormones, and the environment. Steroid hormone levels are markedly different in men and women throughout most of the life span. Steroids can impact the sexual differentiation of the brain and help to transcribe or repress genes in certain cells.

However, hormones are not the only influence that dictates sex differences. Genes can also exert epigenetic effects that can cause sex differences to endure. While sex chromosomes can have an impact on sex differences, researchers have found that other chromosomes can also be related to sex differences.

Sex differences have also been observed in brain cells. For example, microglia, which can both build and destroy synapses, exist in different numbers in the same area of the brain in female and male individuals. Microglia interact with T-cells to modulate pain in a sex-specific manner. In addition, microglia can also amplify signals making them endure for longer periods of time.

Sex differences have also been found in mast cells. Mast cells, which originate in the bone marrow from myeloid precursors, migrate to all body tissues including the brain. They are central to allergic response and are considered the "first responders" after injury. During the first weeks of life, males have more mast cells in certain brain regions compared with females.

Despite these differences, one should not conclude that there are distinct "male" and "female" brains, as researchers have found that some brain areas are considered to be the same in both females and males. Instead, the brain is believed to be more like a "mosaic." Using this paradigm, one can have females that have areas of the brain that are more (or less) masculinized and males can have regions of the brain that are more (or less) feminized.

While there are differences in female and male brains, anatomy is not considered destiny. Behavior cannot be predicted by sex differences in structure or physiology alone. Behavior is only loosely anchored to neuroanatomy and it is buffered by context, experience, current physiology, and gender.

Given the brain sex differences discussed above, it is logical that research studies involving this complex organ should take into account the impact of sex if researchers are to apply some findings exclusively to females or males. The scientific findings and discussions on sex differences presented during this

conference are summarized below. They are instrumental in helping to identify gaps and priority areas for future TBI research.

Session I: Sex Differences in TBI across the Lifespan

Lisa Begg, DrPH, RN, Office of Research on Women's Health, NIH (Moderator)

The Epidemiology of Sex Differences in the Incidence of TBI

Matt Breiding, PhD, Centers for Disease Control and Prevention

Dr. Breiding presented epidemiological data on TBI-related emergency department (ED) visits, hospitalizations, and deaths in the U.S. for 2014. He also discussed Intimate Partner Violence (IPV)-related TBI estimates. Dr. Breiding said that nearly 2.9 million TBI-related ED visits, hospitalizations, and deaths occurred in 2014. Females comprised approximately 49% of all TBI-related ED visits, 41% of TBI-related hospitalizations, and 27% of TBI-related deaths. The leading causes of ED visits and hospitalizations were falls (53.5% and 62%, respectively). Visits to emergency departments related to TBI increased by 980,000 from 2006 to 2014. In the same period, there was an increase in the number of TBI-related ED visits due to falls, with females having an 89% increase and males a 70% increase.

Dr. Breiding said there are no national TBI prevalence estimates as a result of IPV. However, studies in shelters or emergency departments show that 30% to 74% of those women have a history of TBI. In addition, approximately 6 million women have reported being knocked out after getting hit, slammed against something, or choked by their partner. A national survey has also shown that approximately 24% of women have experienced some sort of physical violence from an intimate partner in their lifetime, compared with approximately 13% of men.

Takeaways

- There were nearly 2.9 million TBI-related ED visits, hospitalizations, and deaths in 2014.
- The leading causes of ED visits and hospitalizations are falls.
- There was a significant increase in the number of TBI-related ED visits due to falls from 2006 to 2014 (an increase of 980,000 visits).
- There are no national IPV-related TBI prevalence estimates.
- However, studies in shelters or emergency departments show that 30% to 74% of those women have a history of TBI.

Sex Differences in Pediatric Cases of TBI

Courtney Robertson, MD, Johns Hopkins University

Dr. Robertson explained that trauma is the leading cause of death in children under 18. Approximately 500,000 children under 14 visit the emergency department with a TBI-related injury every year. A 2004 university hospital study involving nearly 16,400 TBI patients under 19 showed that boys had a shorter length of stay in ICUs and girls presented worse outcome trends. A 2013 study of approximately 20,200 teenagers showed lower mortality in pubescent (13-18) girls. In the area of sports-related TBI, women showed a higher rate of symptom reporting than males.

A 2017 study in male and female mice found that both sexes showed reduced sociability 8 weeks after TBI, with males having a decrease in social recognition and females an increase in social avoidance. A 2016 study showed that cerebral blood flow autoregulation was more impaired in male newborn piglets after TBI. Also, norepinephrine was found to be protective in both male and female juvenile piglets. Unpublished data by Dr. Robertson showed sex differences in response to 20-HETE inhibition after TBI. Findings also showed a reduction in lesion volume 3 and 30 days after injury in males.

Takeaways

- Sex differences were found in functional outcomes and mortality after pediatric TBI.
- Potential sex differences were found in concussion recovery time in teenage athletes.
- Findings in adolescents may be influenced by systemic sex hormones.
- “Pediatric” animal models have demonstrated sex-based differences.
- It is important to evaluate male and female animals separately in pediatric TBI studies.

[Sex Differences in Older Adults following TBI](#)

Angela Colantonio, PhD, University of Toronto

Dr. Colantonio presented information on older adults and TBI. There has been a significant increase in TBI-related emergency department hospitalizations among older adults, with women having the highest rates of hospitalization. Also, women 65 and older have the highest rates for diagnosed mild TBI. Falls are the major cause of injury, particularly among women. Dr. Colantonio said that her review of the literature found that older adults with TBI showed poorer functional outcomes and slower recovery. She explained there is a need for evidence-based guidelines, common data elements, and prognostic models.

In a 2010 study by Dr. Colantonio of 306 individuals post-injury, women reported more headaches and dizziness as well as increased loss of confidence compared with men. The symptoms more likely to affect daily functioning among women were the ability to initiate daily activities, high sex drive, and a need for supervision and assistance. Studies have also shown that more older adults experience multiple co-occurring comorbidities as well as higher mortality rates compared with younger individuals. The most frequent comorbidities were circulatory, nervous system, endocrine, nutritional, and metabolic/immune system comorbidities.

Takeaways

- There has been a significant increase in TBI hospitalization in older adults.
- Women 65 and older have the highest rates for diagnosed mild TBI.
- Falls are the major cause of injury, particularly among women.
- Studies have shown that older women report more headaches and dizziness than men.
- Older adults experience multiple co-occurring comorbidities as well as higher mortality.
- There is a need for evidence-based guidelines, common data elements, and prognostic models for this population.

[Highlights of Session I Discussion](#)

- Some preclinical research shows that the method of patient transport to the hospital may

impact outcomes.

- Some of the literature shows that depression symptoms can be protracted for women and girls.
- Further preclinical investigation might be needed to determine the best clinical intervention based on sex, age, and type of injury.

Session II: TBI as a Consequence of Intimate Partner Violence

Katherine Price Snedaker, LCSW, PINK Concussions (Moderator)

TBI in Abused Women from Head Injuries and/or Strangulation: It's all One Brain

Jacquelyn Campbell, PhD, RN, Johns Hopkins University

Dr. Campbell's presentation focused on the effects of TBI on abused women. Intimate Partner Violence (IPV) impacts 20 million Americans every year. One must keep in mind that in contrast to accidents, IPV TBI is often repetitive, with multiple violent attacks over time, often for years. Head injuries in abused women can lead to cognitive and emotional disabilities as well as long-term central nervous system sequelae. Unfortunately, women often do not disclose IPV at the emergency department (e.g., they may report they fell).

Dr. Campbell described a recently published comparative study in the *Journal of Women's Health* that examines abused women versus never-abused controls. The African Caribbean African American Women's (ACAAWS) Study recruited 538 abused women from Baltimore and the Virgin Islands from primary care, prenatal, or family planning clinics, along with 356 controls. Abused women presented nearly twice as many head injuries as controls. They also reported more facial, dental, and eye injuries, as well as broken/dislocated jaws and ear damage. Other than headaches, abused participants reported significantly more central nervous system (CNS) symptoms including memory loss, blacking out, dizzy spells, seizures, vision/hearing problems, and difficulty concentrating.

Takeaways

- Abused women are not always examined for TBI in the emergency department, primary care, and behavioral health offices.
- Unlike accidents, IPV TBI is often repetitive, with multiple violent attacks over time.
- In a recent study, abused women presented nearly twice as many head injuries as controls.
- Abused participants reported significantly more CNS symptoms.
- Future research is needed in the following areas:
 - Research on multiple injuries, IPV, childhood TBIs, and history of child abuse/neglect
 - Research that measures both strangulation and head injuries to sort out the effects
 - Research to examine the interplay among neurological, physiological, and psychological mechanisms

Lessons from Neuroimaging Studies of Women Experiencing Partner-Related TBI

Eve Valera, PhD, Harvard Medical School

Dr. Valera's research focuses on the sequelae resulting from TBI experienced through IPV. Women who are physically abused by their intimate partners can experience various issues including physical

(migraines, broken bones), psychological (higher rates of depression, anxiety, PTSD), and cognitive (memory, concentration) issues. Dr. Valera developed a Brain Injury Interview using established definitions to determine if alteration of consciousness had occurred, such as blacking out. She also established measures to determine the frequency, severity, and recency of the brain injuries, resulting in a Brain Injury Score (BIS). Dr. Valera then interviewed 99 women in both shelter and non-shelter environments. A total of 74% of participants sustained some type of IPV brain injury, whereas only 27% sustained accident-related brain injuries. Additionally, approximately 50% of women sustained multiple brain injuries, with a substantial percentage of them resulting from being strangled.

The BIS was associated with cognitive measures such as memory, learning, and cognitive flexibility. These relationships were independent from the individuals having PTSD or suffering from anxiety. TBI imaging studies involving IPV victims showed an association of neural damage in brain regions highly susceptible to axonal injury from rapid biomechanical forces resulting from head impacts, similar to that experienced in some contact sports. Dr. Valera explained that few imaging IPV studies have been performed.

Takeaways

- Partner-abused women are a unique group of TBI sufferers due in part to the impact of repetitive injuries over time and strangulation.
- Partner-related brain injuries were associated with poorer memory, poorer cognitive abilities, and greater rates of depression.
- The effects of these types of brain injuries likely hinder women's abilities to free themselves from IPV situations.
- The data presented are preliminary but highlight the critical nature of this issue.
- More data are needed to better study IPV TBIs.

[Biomarkers that Reflect Cumulative Head Injuries](#)

Jessica Gill, PhD, RN, NIH National Institute of Nursing Research

Dr. Gill's presentation focused on blood-based biomarkers associated with multiple TBIs. She said that some athletes sustaining multiple TBIs and concussions go on to develop Chronic Traumatic Encephalopathy (CTE). The neurons in these individuals show an accumulation of tau and amyloid depositions, similar to that found in Alzheimer's disease symptoms and pathology. When a neuron is physically damaged, tau proteins are released into the cerebrospinal fluid and eventually into the blood. High concentrations of these proteins are linked to mortality after severe TBIs as well as prolonged recovery. Dr. Gill examined tau plasma concentrations in three cohorts: athletes experiencing concussions, military personnel with chronic symptoms, and military personnel exposed to blasts. The last can be compared with loss of consciousness due to strangulation during IPV.

Tau levels were elevated in military personnel experiencing at least one TBI, compared with controls. Multiple (three or more) TBIs were related to higher total tau levels, which in turn were associated with chronic symptoms. High blast exposures were also associated with higher tau levels. In athletes, having an elevation of tau six hours post-concussion was related to a longer Return to Play. In a civilian study supported by the Center for Neuroscience and Regenerative Medicine, more women presented damage as identified through imaging compared with males. Women were also more likely to present symptoms in the Neurobehavioral Symptom Inventory; however, no biomarker differences were found at baseline

based on gender. Studies on a different biomarker, GFAP, did show differences based on gender. GFAP levels were also found to be a good predictor of recovery.

Takeaways

- Individuals who presented cumulative head injuries showed increased presence of biomarkers in their blood.
- Tau concentrations were found to be higher in those with multiple TBIs, including blast injuries.
- Tau concentrations related to higher symptoms, both neurological and behavioral.
- Higher tau concentrations were related to prolonged recovery in athletes.
- Acute changes in tau may relate to gender, but more data is needed to ascertain this.
- Future research questions include:
 - Are we looking at the right set of biomarkers? Could other biomarkers be involved?
 - How can we use biomarkers to understand neuronal damage and cognitive changes?
 - How can we identify women most at risk using biomarkers?

IPV-Related TBI among Women Veterans: Evidence to Inform Patient-Centered Identification and Intervention

Katherine Iverson, PhD, Boston University

Dr. Iverson explained that women veterans are the fastest-growing population of veterans in the Veterans Health Administration (VHA). In 2017, more than 700,000 women veterans were enrolled in VHA care. Approximately 10% of the women in the Iraq and Afghanistan conflicts screened positive for deployment-related TBI. Lifetime IPV among women veterans was higher compared with that of non-veterans (33% to 23.8%, respectively). Dr. Iverson provided findings on two of her studies. The first study was a regional mail survey (n=176) using a modified VA TBI screening tool to identify the occurrence of self-reported IPV-related TBI. The study also examined the associations of IPV-related TBI with mental health symptoms and VA health care use. The second study was a web-based survey (n=224) using a screening tool to identify the occurrence of IPV-related head events and IPV-related TBI history in women veterans who experienced lifetime IPV. The study also examined the associations among IPV-related TBI with IPV-related PTSD diagnosis and symptoms.

In the first study, the regional mail survey, approximately 69% of the women reported being hit on the head, 63% being pushed or shoved, 63% being strangled by an intimate partner, and 12% having broken teeth. More women who had an IPV-related TBI reported PTSD symptoms compared with women who had an IPV-related event but no TBI (53.2% vs. 34.1%, respectively). Also, more women who had an IPV-related TBI reported depression compared with women who had an IPV-related event but no TBI (26.6% vs. 20.7%, respectively). IPV-related TBI was associated with higher VA health care utilization including a greater volume of past-year VA health care use, more ER visits for medical and mental health problems, and more outpatient and inpatient mental health visits. Dr. Iverson explained that the ER and inpatient mental health departments would be good places to screen for IPV-related TBI. The second study, the web survey, found that women with IPV-related TBI with current TBI symptoms were 5.9 times more likely to have probable IPV-related PTSD than women with no IPV-related TBI.

Takeaways

- Women veterans are a sub-population at high risk for IPV-related TBI.
- IPV-related TBI among women veterans is associated with high volumes of VHA health care use, especially ER and mental health visits.
- PTSD symptom profiles are somewhat different for women veterans with IPV-related TBI with current TBI symptoms.
- Researchers and clinicians should use caution when attributing overlapping symptoms to PTSD and consider TBI comorbidity when addressing IPV.
- The ER and inpatient mental health departments could be good places to screen for IPV-related TBI.

Highlights of Session II Discussion

- There are very little data and studies that make the connection between IPV-TBI, imaging, and cognitive/psychological function.
- In general, women tend to over report TBI symptoms, but it is not clear whether this is a sex difference *per se*. Over reporting of symptoms has also been seen in women with PTSD and depression.
- Women with IPV presented more inflammation (i.e., higher cytokine levels) than controls.
- Individuals who have experienced trauma and developed PTSD or depression have higher levels of cytokines related to cardiovascular, obesity, and other risk factors.
- Dr. Valera said that some of the women that were excluded in her study also had a history of seizures. Further research is needed to determine if women who present with first-time seizures at emergency departments actually have a hidden TBI.
- According to Dr. Valera, the number of women who sustain IPV-related TBIs exceeds the number of individuals in the NFL or the military sustaining TBIs. However, IPV-related TBI research is not so well funded as sports- or military-related TBI research.

Session III: Lost in Translation: Sex Differences in Preclinical and Clinical Research

Jeremy Brown, MD, National Institute of Neurological Disorders and Stroke, NIH (Moderator)

Progesterone for the Treatment of Traumatic Brain Injury (ProTECT)

David Wright, MD, Emory University School of Medicine

Dr. Wright described the efforts of the ProTECT trial. ProTECT was a single center, phase III, randomized clinical trial of progesterone for acute TBI held at Grady Memorial Hospital in Atlanta. The trial involved about 440 individuals ages 18 and older with blunt TBI and a Glasgow Coma Scale score between 4 and 12. Progesterone came about as a potential therapy as it has been linked to reducing cerebral edema and inflammatory cytokines. In addition, more than 200 studies have shown positive results with progesterone in neurological injury in animal species. Unfortunately, the study was stopped at an interim analysis showing that favorable outcomes (48.2%) were similar to placebo (52.7%). Also, mortality did not show a significant difference against placebo. A subgroup analysis showed that women

did worse with progesterone treatment, but this finding was not significant.

Dr. Wright offered some recommendations for future clinical trials. He suggested that preclinical trials involve multiple animal models. Animal clinical trials should also be conducted at various centers (multi-center) to ensure reproducibility. Translational programs need to identify timing, window, and dose as part of the treatment studied. Also, patients could be better selected with respect to the type and grade of TBI in order to decrease subject heterogeneity. Pharmacodynamic and phenotypic biomarkers could be developed to determine optimal dose and injury severity. It would be helpful if one could determine if there is a group of individuals who respond better to treatment. Dr. Wright also suggested considering larger phase II trials (phase IIb) and smaller phase III trials for TBI studies.

Takeaways

- Consider conducting larger, multi-center preclinical trials.
- Identify timing, window, and dose as part of the treatment in trials.
- Identify the general pathways affected by the treatment.
- Develop biomarkers that can assist in translation from animal models into humans.
- Better select trial patients (e.g., type and grade of TBI).
- Identify the group of patients who are responding well to treatment.
- Conduct larger phase II and smaller phase III trials.

Transforming Research and Clinical Knowledge in TBI (TRACK-TBI)

Harvey Levin, PhD, Baylor College of Medicine

Dr. Levin presented preliminary findings of the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) multi-center pilot study. The trial's goal is to examine sex differences and age effects in cognitive, neurobehavioral, and quality of life outcomes at 6 months after mild TBI. The group studied involved 100 patients who were stratified by sex and age (18-29 and 30-39 years).

Six-month global outcome data showed more severe disability in women than men whereas severity of acute injury and mechanism (e.g., assault) did not differ by sex. No sex differences were significant for processing speed, memory, or executive function. Examination of the data by sex and age showed that women in the 30-39 year age range had more severe disability, PTSD symptoms, and Post-Concussion Syndrome at 6 months after mild TBI than either men or women ages 18 to 29. Individuals in the younger age group (18-29) had less severe generalized distress, and lower level of PTSD symptoms than the older (30-39) group.

Takeaways

- In a pilot study involving mild TBI, some differences were found when stratifying by age and sex.
- Women showed more severe disability compared with men.
- Women in the 30 to 39 age group had more severe disability, PTSD, and Post-Concussion Syndrome 6 months after mild TBI compared to both younger women and men.
- Individuals in the younger age group (18-29) had less severe generalized distress and a lower level of PTSD symptoms than the older (30-39) group.

Approaches and Decisions in Acute Pediatric TBI (ADAPT) Trial

Michael Bell, MD, Children's National Health System

Dr. Bell explained that significant differences in the treatment approaches for pediatric TBI still exist. To address this variability, the Approaches and Decisions in Acute Pediatric TBI (ADAPT) trial was developed. The trial will focus on comparing the effectiveness of various treatment strategies in the real world. Sites can care for children in their own way and the variability is then measured and corrected statistically. The trial will enroll 1000 children in 51 sites (34 in the U.S. and 17 international). The primary outcome will be the Glasgow Coma Scale E-Peds at 6 months. Three major strategies will be examined:

- Intracranial hypertension therapies – CSF diversion, hyperosmolar therapies
- Secondary insults – hypoxia, hyperventilation without intracranial hypertension
- Metabolic approaches – nutrition strategies, glucose management

In a preliminary analysis of the first 200 patients enrolled, females presented slightly more abuse cases, but this group did not have a significantly higher incidence of death. Data were stratified by G scores into three groups: GCS scores of 3, 4-5, and 6-8. The odds ratio of death was 11 times higher for GCS scores of 3 vs. 6-8. Data were also stratified by age, race/ethnicity, method of transportation to the hospital, type of injury, cause of injury, mechanisms of injury, injury severity, and other groupings. Data have been analyzed but remain unpublished. The trial will be renewed to further examine the data by sex.

Takeaways

- There is a significant amount of variability in TBI pediatric treatments.
- The ADAPT trial will examine the effectiveness of three strategies: intracranial hypertension, metabolic approaches, and secondary insults.
- It was suggested that trials control for GCS scores (in the ADAPT trial participants are divided into three groups) as mortality can be significantly different in each of these groups.
- It was suggested that researchers stratify the data by sex as well as other subgroups such as type of injury, cause of injury, mechanisms of injury, injury severity, and other groupings.

The Unique Challenges Facing Preclinical to Clinical Translation in TBI Research

Donald Stein, PhD, Emory University

Dr. Stein discussed the challenges facing preclinical to clinical translation in TBI research. There are physiological differences in females that can affect drug kinetics including higher percentage of body fat, less blood volume, lower plasma protein binding, lower hepatic biotransformation of drugs, and slower renal clearance. There also are sex differences in the gross and cellular brain anatomy of females and males. Sex differences in glia reactivity after cortical brain injury were found. This suggests that male and female mice have different neuroinflammatory responses after a cortical injury and that sex differences in reactive gliosis may contribute to sex differences in neuroinflammatory diseases. Early observations in TBI also show that females with high levels of progesterone at the time of injury had better outcomes.

With respect to trials, dosing, duration, vehicle, route of administration, and timing of treatment may

impact outcomes. The failure to perform preliminary dosing optimization can confound both animal and clinical trial outcomes. Also, the route of administration and duration of treatment have different consequences in scaling up from rodents to people. Dr. Stein emphasized that better selection procedures are essential. Dr. Stein made the following suggestions for NIH:

- Consistent budgetary support is needed for studying both males and females in preclinical and basic research on TBI.
- Long-term studies of multiple functional outcomes and sex differences are more relevant to patients and their caregivers than biomarkers.
- The overwhelming emphasis on first determining mechanisms before safety and efficacy should be reconsidered and perhaps reversed for translational research.
- Magic bullet approaches to treatment development should be reconsidered in light of all the failures.
- More attention is needed to sex differences and hormonal status at time of injury.

Takeaways

- Sex differences should be considered in both animal and human studies.
- Dosing, duration, vehicle, route of administration, and timing of treatment may impact outcomes.
- Researchers should be less inclusive and more focused on selection and classification of patients.
- The “magic bullet” approach seeking drugs that target just one mechanism hasn’t worked. Also, targets may not be the same for males and females.
- Unambiguous markers of functional recovery and surrogate markers for CNS repair remain to be defined.
- More attention to combination therapies and pleiotropic agents is needed.

[Sex Differences as Revealed by Research on Large Animal Models of TBI](#)

Candace Floyd, PhD, University of Utah

Dr. Floyd’s presentation made the case for the use of porcine models. Porcine models may be better for studying TBI than rodent models because of their boney skull structure, gray/white matter distribution, and brain anatomy. Unlike rodent models, the porcine brain is similar to the human brain in that it contains gyri and sulci (folds). The presence of gyri affects brain movement during a TBI, and more brain deformation has been found in gyrencephalic brains. Porcine models can also be used to determine injury as well as injury severity, impact on memory, and impact of anxiety. The estrus cycle is also comparable in the pig and human, while the cycle on the rodent differs significantly.

Dr. Floyd presented unpublished results of a study on sex differences in recovery after spinal cord injury in adult Yucatan pigs. Models received a T10 contusion/compression spinal cord injury with three outcomes measured at 48 hours and 6 weeks: hind-limb locomotion, tissue sparing, and inflammatory cytokines. The study measured the impact of high/low levels of estradiol on recovery. Interleukin-6 cytokines were significantly higher in females with low estradiol compared with females with high estradiol or males. This showed that the estrus cycle can impact early pathophysiology. Other findings showed that males had a higher preservation of neurons (gray and white matter) at the spinal cord injury epicenter 48 hours after injury compared with females. Also, 6 weeks after injury the differences

in white matter sparing at the injury's epicenter were very subtle. There were no significant differences in locomotor recovery.

Takeaways

- Sex differences were observed 48 hours after injury in porcine spinal cord injury models.
- Interleukin-6 cytokines were significantly higher in females with low estradiol compared with females with high estradiol or males.
- Therefore, levels of estradiol relative to the estrus cycle might impact the early pathophysiology.

The Role of Hormones in Response to Trauma

Ann Rasmusson, MD, Boston University School of Medicine

Dr. Rasmusson said that allopregnanolone and pregnanolone (“ALLO”) are synthesized in the brain, adrenal glands, and ovaries. ALLO has a very broad impact and can act as an anxiolytic, antidepressant, anticonvulsant, neuroprotector, and regenerator. ALLO is critical for myelination, supports neurogenesis, and protects against ischemic and blunt trauma-induced brain injury. In addition, allopregnanolone acts at both synaptic and extrasynaptic GABA_A receptors.

Studies were conducted in women during the follicular phase of menstruation when progesterone levels are low and stable. Results showed that ALLO levels were only 39 percent of normal in women with PTSD compared to healthy controls. Studies also showed that healthy women increased their levels of ALLO when moderately stressed whereas this did not happen in women with PTSD. This suggests that the neuroprotector could also be low in individuals with TBI and PTSD, and potentially be associated with negative outcomes. Researchers also measured the ratio of ALLO to DHEA and found that it could be a predictor of negative outcomes. In men, the ratio of ALLO to DHEA correlated with dysphoria.

Takeaways

- ALLO levels are lower in women with PTSD compared with healthy controls.
- Healthy women increase ALLO levels when moderately stressed compared with women with PTSD. This suggests that the neuroprotector could also be low in individuals with TBI and PTSD, and potentially be associated with negative outcomes.
- ALLO levels may be low during moderate stress in individuals with TBI and PTSD and may be potentially associated with negative outcomes.
- The ratio of ALLO to DHEA can be a predictor of negative outcomes.

Highlights of Session III Discussion

- Due to a change in schedule, no discussion occurred for this session.

Session IV: Sex Differences following Sports-Related TBI

Pat Bellgowan, PhD, National Institute of Neurological Disorders and Stroke, NIH (Moderator)

Epidemiology of Sex Differences in Sports-Related Concussion

Dawn Comstock, PhD, University of Colorado School of Medicine

Dr. Comstock said that over the past 15 years there has been an explosion of journal articles reporting epidemiological data on sports-related injuries. Unfortunately, most of these articles focus on competitive sports within the school setting leaving out younger athletes and recreational sports. Nonetheless, current data show that most of the sports with the highest concussion rates have a strong gender bias (e.g., boxing, football, ice hockey). Football has the highest concussion rates compared with any other sport, with girls' soccer following in second place. Overall, males sustain higher numbers of sports-related concussions than females across all ages. However, in gender-comparable sports (such as soccer, basketball, and baseball/softball) females have higher concussion rates than males.

While there are gender differences among concussed athletes, some gender differences have narrowed over time and appear to be shirking, such as the rates of post-concussion amnesia, disorientation, and loss of consciousness among girls and boys. On the flip side, irritability, noise sensitivity, and light sensitivity have increased for both boys and girls over time. Other studies have shown that both male and female athletes decreased their Return to Play in all three categories (<1 day, 1-2 days, 3-6 days) from 2016 to 2008. However, some gender differences exist in gender comparable sports. Dr. Comstock offered a set of recommendations at the end of her talk (listed below).

Takeaways

- Football has the highest concussion rate of any sport, followed by girls' soccer.
- However, in gender-comparable sports, females have higher concussion rates than males.
- For both boys and girls, the rates of reported post-concussion symptoms such as amnesia, disorientation, and loss of consciousness have decreased.
- On the flip side, irritability, noise sensitivity, and light sensitivity have increased for both boys and girls over time.
- More funding is needed as there is no federal funding for sports-related injury surveillance besides CPSC NEISS ED cases.
- There is little or no national data on younger athletes, recreational sports, or traditionally understudied populations (e.g., rural, low SES athletes, transgender athletes, etc.).

Sex-Related Challenges after Sports Concussion in Pediatric Patients

Christopher Giza, MD, University of California, Los Angeles

Dr. Giza reviewed a wide variety of studies on pediatric sports concussions. In the area of basic science, studies show less acute inflammation but greater axonal damage as well as fear behavior after TBI in females. Developmental sex comparisons have not been done after repeated mild TBI. Some studies suggest that pituitary dysfunction can occur after repeated mild TBI and this may result in sex-related sequelae.

In the clinical arena, females seem to report more symptoms than males. However, in younger children

more boys are reporting symptoms at baseline than girls. A retrospective study of children aged 10-17 in pediatric sport concussion clinics found that females had longer recovery times. Another study in sports concussion clinics supported this by showing that males had faster recovery. Dr. Giza also posed some questions regarding rules/policy for the audience to mull over. For example, he asked if we should have an age at which sex-specific rules should be implemented. Also, should specific sports require sex-specific protective equipment?

Takeaways

- There are little or no comprehensive data or studies on children under middle school age related to sports concussions.
- Basic science studies show less acute inflammation but greater axonal damage in females.
- Females in their teens seem to report more symptoms than males, but younger boys report more symptoms than females at baseline.
- Females have longer recovery times than males after a concussion.
- Future studies with sex-specific hypotheses should be conducted.

Sex Differences in Recovery from TBI among High School Athletes

Harvey Levin, PhD, Baylor College of Medicine

Dr. Levin presented a series of studies on the recovery of high school athletes after TBI. A 2005 study showed lower female cognitive scores following a sports-related concussions compared with males. A 2012 longitudinal study of 222 athletes in high school and college showed more reported symptoms in female athletes than in males at 2, 7, and 14 days following injury.

Female athletes performed worse than males in the area of visual memory. However, there were no sex differences in verbal memory, motor processing speed, or reaction time composites. A separate study showed that a visual memory deficit was related to delayed Return to Play in female but not male adolescent athletes. A 2017 study showed that recovery of oculo-vestibular function and dizziness was slower in females in one longitudinal study, but replication is needed to ascertain this. A study also showed that the risk of having a short intermenstrual interval was increased (16%) after a sports-related concussion.

Takeaways

- Most studies report more severe and persistent post-concussion symptoms in female than male adolescent athletes.
- Recovery of oculo-vestibular function and dizziness was slower in females in one longitudinal study, but replication is needed to ascertain this.
- Sex differences in cognitive effects are less consistent across studies; visual memory was more affected in female than male adolescents in two studies.
- Menstrual patterns can be affected after a sports-related concussion.
- Mechanisms of sex differences in recovery need to be better understood, and preclinical research may help elucidate such mechanisms.

Current Trends Related to Sex Differences from the Concussion Assessment, Research and Education (CARE) Consortium Study

Michael McCrea, PhD, Medical College of Wisconsin

Dr. McCrea presented data on the NCAA-Department of Defense CARE consortium. The consortium provides data from both NCAA athletes and military academy cadets. The study is being performed in 30 sites and enrolls close to 39,000 athletes (mean average 19) with 2661 athletes reporting concussions. Data collected included neurocognitive and behavioral testing, blood biomarkers, DNA, and MRI studies. However, not all of these types of data were collected in all athletes. Some of the data presented were not yet published and are therefore not included in this report.

A preliminary review of some of the data showed a higher rate of concussions in females playing soccer and water polo compared with men. Males reported significantly higher rates of symptoms such as loss of consciousness, post-traumatic amnesia, and altered mental status. There were no differences in the clinical recovery time between males and females, although females showed slightly longer Return to Play (RTP) time. Similar factors were found to predict recovery and RTP in females and males, namely: acute injury characteristics, acute assessment results, and the individual's pre-injury health history. Research is also showing robust signal abnormalities in biomarkers and imaging 24 hours post-injury. These signals seem to persist beyond the time of clinical recovery.

Takeaways

- A higher rate of concussions was seen in females playing soccer and water polo.
- Males reported significantly higher rates of symptoms such as loss of consciousness, post-traumatic amnesia, and altered mental status.
- No differences in the clinical recovery time were found between males and females.
- A slightly longer RTP time was seen in females.
- Similar factors were found to predict recovery and RTP in females and males.

Highlights of Session IV Discussion

- More research is needed to determine what factors can put a person at risk for persistent symptoms after a concussion.
- Dr. McCrea said there is variation in the RTP duration among the various sites studied. There is additional variation within an individual site based on clinical treatment (i.e., based on the clinician treating the patient).
- In clinical research, common data elements can greatly facilitate communication across centers and also assist in the replication of studies.
- Dr. McCrea said that future studies will compare concussed, exposed, and control cohorts to determine if there was a meaningful change in their academic performance over the past 4 or 5 years.
- Very little data are available on academic performance after a sports-related concussion on high school, middle school, or grade school students in part due to the stringent FERPA laws restricting access to grades.

Introduction to Day Two

Janine Clayton, MD, Director, Office of Research on Women's Health, NIH

Dr. Clayton opened the second day of the conference by stating the importance of the conference and its breadth in terms of the topics covered. She provided a summary of the first day of the conference and briefly discussed the topics for the second day. She also said the workshop is very important in identifying TBI sex differences as well as future areas for TBI research.

Session V: Military Perspective: Sex Differences in TBI among Service Members and Veterans

Katherine Helmick, MS, Defense Centers of Excellence for Psychological Health (Moderator)

Sex Differences in Post-Concussion Symptom Reporting among Service Members and Veterans

Sara Lippa, PhD, Walter Reed National Military Medical Center

Dr. Lippa presented results of various studies of TBI in the military. A 2011 study by Iverson of 12,605 veterans (5.2% female) showed that women were more likely to report severe or very severe post-concussion symptoms, be diagnosed with alcohol-related disorders, or be diagnosed with depression or PTSD with comorbid depression. In 2013, Iverson conducted another study of 2,348 veterans (51% female) both with and without a history of TBI. TBI was associated with a higher odds ratio of reporting anxiety and physical symptoms in both men and women, with women having higher odds ratios than men. In the same study, women without PTSD were also found to have a higher odds ratio of depression and alcohol use when compared with men.

In 2017, a study was conducted by Brickell of 86 female and 86 male closely matched service members with a history of mild TBI diagnosis. In this study, women reported significantly more post-concussion and PTSD symptoms than men. A 2018 study by Dr. Lippa involving 79 female and 79 male individuals with history of mild TBI diagnosis (from the same group as above) showed that PTSD explained a significant portion of the variance of post-concussion symptoms. In this study, TBI severity and bodily injury were not significantly related to the overall report of post-concussion symptoms and, unlike previous studies, sex was not significantly related to the overall report of post-concussion symptoms.

Takeaways

- Despite increasing involvement of women in the military and in combat roles, many military studies include only a very small proportion of females or exclude females altogether.
- Post-concussion symptoms are subjective and non-specific, and objective outcome measures specific to TBI should be emphasized.
- Three out of four of the studies presented above suggest that women report more cognitive, affective, somatosensory, and vestibular symptoms than men.
- When controlling for symptom validity and PTSD severity, these relationships are attenuated, with only some women reporting more somatosensory and vestibular symptoms than men.
- When assessing post-concussion symptoms and other self-reported outcomes, it is imperative to control for PTSD and symptom validity.

Sex Differences in Outcomes of Service Members after Polytrauma/TBI

Odette Harris, MD, MPH, Stanford University

Dr. Harris said there are more than 1.8 million women veterans today. She explained that in many TBI studies, women make up only a small proportion of participants. Dr. Harris led a retrospective cohort analysis of women treated at Palo Alto Polytrauma System Care (PSC) clinics with a diagnosis of TBI. Data collected included injury etiology and injury characteristics as well as social characteristics and changes since injury (i.e., housing, marital status, job, children, military status, substance abuse). These women were compared with the aggregate data of studies in the literature (“TBI cohort”) where some of the studies included men.

The comparison showed more homelessness among women with mild TBI compared with the general TBI cohort (11% vs. 2%, respectively). More women with mild TBI were likely to be diagnosed with depression, PTSD, anxiety, substance abuse, and cognitive disorders/impairments compared with the TBI cohort. Women with mild TBI reported more chronic pain, chronic headaches, sleep disturbances, and neurological problems than the TBI cohort. They also suffered more severe somatosensory and vestibular symptoms when compared with men with TBI. A cross-sectional analysis of the women matched to men was carried out at the Palo Alto PSC clinics. Similar to the comparison study, the cross-sectional analysis showed that women reported significantly increased somatosensory and vestibular symptoms. However, longitudinal results did not support the cross-sectional findings both in the general and in the matched cohort. Dr. Harris said that more data are needed to more precisely understand interventions in women.

Takeaways

- Comparison studies showed differences between veteran women and the general mild TBI literature population, although this was not always supported by other analyses.
- Comparison studies found a larger percentage of homeless veteran women compared to the TBI literature population. These women were also more often diagnosed with depression, PTSD, anxiety, substance abuse, and cognitive disorders/impairments.
- Women studied reported more chronic pain, chronic headaches, sleep disturbances, and neurological problems and suffered more severe somatosensory and vestibular symptoms than the TBI literature population.
- Multi-dimensional measures (i.e., functional and biological) need to be collected to provide precise targets for treatment and management. More outcomes also need to be identified that reflect rehabilitation processes that are specific to women.

Trajectories of Comorbidity among Male and Female Veterans and Service Members after TBI

Mary Jo Pugh, PhD, University of Utah School of Medicine

Dr. Pugh presented a latent class analysis of Veterans Administration data stratified by sex. The analysis examined an increase (or decrease) of TBI-related comorbidities over time in veterans. The study included approximately 144,700 men and 20,200 women over a 3-year period. Five overall trajectory patterns were detected: 1) individuals who were relatively healthy, 2) individuals who started healthy but turned to a Polytrauma Clinical Triad (i.e., TBI, PTSD, and pain), 3) a mental health group with pain, 4) individuals with pain, and 5) individuals who had a Polytrauma Clinical Triad (PCT). Two other patterns

were found. One pattern was only for men who started with PCT and improved over time and another only for women with a mood focus and pain. The data presented have not yet been published and were therefore not presented in this summary.

Over time, in the relatively healthy group, a higher level of depression was seen in women when compared with men. Both men and women had increased PTSD over time. In the second group, both men and women started relatively healthy but developed PCT over time. Women showed increased depression while men showed increased substance use disorder. The mental health with pain group showed high levels of substance use disorder in men. This group also showed high levels of PTSD in both women and men. Women in the PCT group did not show major increases of other comorbidities over time except for PTSD, pain, and obesity. The group of only women with a mood focus and pain showed high levels of depression and high pain. Finally, the group of only men who started with PCT but improved showed significant decreases in comorbidities over time including PTSD, depression, anxiety, headache, back pain, and other comorbidities.

Takeaways

- Latent class analysis (LCA) can help examine sex differences in comorbidity phenotypes or outcomes.
- Findings from LCA suggest there are many similarities in comorbidity phenotypes between men and women veterans, but also meaningful differences that require more exploration with targeted primary data collections.
- Longitudinal data can improve our understanding of comorbidity evolution and help identify individuals at risk for adverse outcomes early in the course of care.

The Neuropathological Trajectory of Male vs. Female Veterans following TBI

Deborah Yurgelun-Todd, PhD, University of Utah School of Medicine

Dr. Yurgelun-Todd explained the advantages of using clinical neuroimaging to study TBI. One advantage is that it allows researchers to characterize underlying brain changes that correlate with patterns of behavioral change. It also allows researchers to begin differentiating individuals with comorbid syndromes, track their course of recovery, and define treatment effects on brain function. Dr. Yurgelun-Todd presented findings of some imaging studies involving both veterans and civilians. Structural imaging data in TBI indicated changes in cortical thinning, white matter hyperintensities, and diffuse axon injury in heterogeneous, non-focal areas after TBI. The presence of psychiatric comorbidity, particularly PTSD, was thought to exacerbate tissue loss.

In civilian males with mild TBI, a reduction in white matter tract integrity was observed relative to females with mild TBI and controls. Task-based fMRI showed that patients with mild TBI produce areas of both higher and lower brain activation compared to non-TBI patients. Resting state brain connectivity was found to be reduced in patients with mild TBI and was associated with altered cognitive functioning. Orbitofrontal connectivity was found to differ between female and male veterans with TBI. Female connections were more unilateral and more focal while male connections were more widespread. Sex differences were also observed in clinical symptoms with males showing higher physical aggression and revenge planning. This was not seen in female veterans.

Takeaways

- Clinical neuroimaging is useful in TBI research as it characterizes underlying brain changes that may correlate with patterns of behavioral change.
- Civilian males with mild TBI show a reduction in white matter tract integrity compared with females and controls.
- Sex differences were observed in clinical symptoms with males showing higher physical aggression and revenge planning.
- There is a need for standardization of assessment methods and analysis as different research groups are using different approaches, making it difficult to derive conclusions based on the data.
- There is also a need for the systematic and objective evaluation of TBI symptoms and diagnosis.
- Larger study samples and increased inclusion of female study participants are also needed.

Highlights of Session V Discussion

- A suggestion was made for researchers to study the potential association of education levels and outcomes, as women who enlist have on average higher education levels compared with men.
- Research is needed to determine whether PTSD and depression are more common in active duty or veteran women.
- A small study showed that military sexual trauma in both men and women was associated with PTSD.
- Researchers should consider adding skydiving to the sports studied as the opening shock of a parachute might impact the brain.
- A suggestion was made for researchers to consider incorporating trauma across the life course (e.g., physical and sexual abuse) as well as military sexual trauma in their studies.
- Measuring impulsivity and impulse control could serve as an intermediary phenotype and perhaps link to PTSD and impaired emotional regulation.
- Alcohol abuse is often considered in studies, but perhaps researchers should also consider nicotine dependence. Dr. Rasmusson said that data analysis showed that among smokers the clustering of PTSD, depression, and pain had an odds ratio of 3.5, confirming comorbidity.

Session VI: Sex Differences in Diagnosis, Prognosis, and Management of TBI

Alison Cernich, PhD, National Institute of Child Health and Human Development, NIH (Moderator)

Sex Differences in Prognostic Markers of TBI

Rebekah Mannix, MD, MPH, Boston Children's Hospital

Dr. Mannix said that one of the challenges in studying biomarkers is that biomarkers can be both a prognostic marker and an outcome. An example would be the troponin biomarker in myocardial infarction. Dr. Mannix explained that much could be learned from similar research done about stroke and Alzheimer's disease. For example, in Alzheimer's disease there is research looking at gene expression based on sex. A 2017 study analyzed the TRACK-TBI pilot and found that phosphorylated tau

(as well as the ratio of phosphorylated tau to tau) were useful in the diagnosis and prognosis of mild TBI. However, one of the challenges is that only a small number of females were involved in this study.

Dr. Mannix presented the findings of a study involving approximately 1,600 individuals that examined protein expression in biomarkers across various psychiatric diseases. Results showed that expression in various biomarkers differed not only by sex, but also by female hormonal status (menstrual cycle or taking exogenous hormones). A preclinical study of the GFAP biomarkers in repetitive mild TBI showed higher expression of GFAP in the corpus callosum and prefrontal cortex in females with repetitive mild TBI compared with males with repetitive mild TBI. Expression of GFAP was also higher in these areas in females with repetitive mild TBI compared with females with mild TBI. Females also showed differences in depressive-like behavior and locomotion compared with males.

Takeaways

- Protein expression can differ in various biomarkers based on sex and female hormonal status.
- More women studies are needed related to biomarkers and TBI.
- Researchers should look for sex-specific differences to actually find them, starting with preclinical models.
- The biology of TBI may be subject to sex-specific differences—therefore, testing characteristics of putative markers should be studied accordingly.
- Basic epidemiologic questions in sex-specific outcomes in TBI need further study.

[Impact of Menstrual Phase on Outcome after Mild TBI](#)

Jeff Bazarian, MD, University of Rochester School of Medicine

Dr. Bazarian presented a graph showing that the probability of reporting post-concussion symptoms 3 months after TBI is higher among females of childbearing age. He hypothesized that the outcome may be related to the menstrual phase at the time of injury. To test this, he studied women who experienced mild TBI during either the luteal (high progesterone) or follicular (low progesterone) phase of menstruation. The study involved 144 women who were divided into three groups: women in the luteal phase with progesterone levels greater than 2 ng/ml, women in the follicular phase with progesterone levels equal to or less than 2 ng/ml, and women taking synthetic progesterone (birth control). Women who had a hysterectomy or were post-menopausal were excluded from the study.

Results showed that women who were injured in the luteal phase had more post-concussion symptoms 1 month after injury compared with women in the follicular phase or those taking synthetic progestins. Women injured in the luteal phase also reported a lower quality of life. Dr. Bazarian said it is important to keep in mind that some post-concussion symptoms can be similar to pre-menstrual symptoms (e.g., fatigue, nausea, sleep disturbance, trouble concentrating, irritability, restlessness, etc.).

Takeaways

- Women who experience mild TBI during the luteal phase had worse outcomes than women injured during the follicular phase.
- Women taking synthetic progestins had outcomes similar to those injured during the follicular phase.
- The putative mechanism is unclear and deserves further investigation.

- In clinical trials of mild TBI, researchers should consider determining the menstrual phase at the time of injury and controlling for this when determining the effect of treatment on outcomes.

Sex Differences in Inflammation and Imaging

Christine Turtzo, MD, PhD, National Institute of Neurological Disorders and Stroke, NIH

Dr. Turtzo said that most TBI studies of inflammation to date have either not considered—or not been designed—to address sex differences. Dr. Turtzo said that much can be learned from preclinical and clinical stroke studies that have addressed inflammation. In stroke studies, some pharmacological agents (e.g., aspirin) can have different effects depending on the recipient's sex. Sex steroid hormones may also play a role in the inflammation process, although steroid hormones can be proinflammatory or anti-inflammatory depending on timing and the underlying degree of tissue inflammation. Also, other studies have shown that microglia and macrophages display sex differential responses.

A 2017 preclinical study reported sex differences in the inflammatory response after experimental TBI, with early increased microgliosis and astrogliosis in males versus females. The study also found an increased invasion of peripheral macrophages in males. Dr. Turtzo said it is important to keep in mind that patterns of inflammation can vary depending on the type of injury model (e.g., focal contusion vs. diffuse injury model). Therefore, this should be considered by researchers in the future. While preclinical studies comparing responses in male and female animals are invaluable for understanding molecular mechanisms, even the best preclinical models lack the complex injury variations seen clinically. Dr. Turtzo added that neuroimaging can be a useful tool to investigate *in vivo* inflammation, but researchers need a better understanding of the relationship between imaging findings and the underlying neuropathology.

Takeaways

- Sex differences exist in the neuroinflammatory response.
- Stroke studies have shown sex differences in the use of pharmacological agents.
- Sex steroid hormones may be proinflammatory or anti-inflammatory depending on timing and degree of inflammation.
- Patterns of inflammation can vary depending on the type of injury model.
- Most TBI studies of inflammation to date have either not considered—or not been designed—to address sex differences.

Sex Differences in Social Behavior in Rehabilitation and Beyond

Lyn Turkstra, PhD, McMaster University

Dr. Turkstra said that social cognition has grown as a topic of interest in TBI research. It is believed that brain areas that are implicated in social thinking can also be damaged in TBI. A study by Dr. Turkstra estimated that about 30% of adults with moderate-severe TBI have impairments in emotion recognition. Sex differences do exist in this area. After moderate to severe TBI, men have lower scores in emotion response accuracy.

This could be important in TBI rehabilitation because men and women might have different expectations for social behavior, and statistics show that most TBI patients are currently male and the rehabilitation

staff mostly female. Some data also show that social cognition skills might be related to rehabilitation outcomes.

Takeaways

- Data suggests that, overall, women are slightly better than men at recognizing emotions and inferring others' thoughts and feelings.
- TBI can affect emotion recognition, more so in men than in women.
- The extent to which TBI affects every day social cognition is unknown and might be influenced by other cognitive demands.
- Women might have higher expectations for themselves and others, which might interact with outcomes and outcome assessment.
- Research is needed on social cognition and social functioning that considers both performance and expectations.

Highlights of Session VI Discussion

- Rehabilitation guidelines are needed to specify physical therapy and occupational therapy dosing in rehabilitation for TBI patients.
- A participant suggested that the research information presented during the workshop, as well as other TBI resources, be disseminated to the TBI patient population.

Session VII: Prioritization of Research Needs: Breakout Sessions

Upon conclusion of the presentations, invited speakers congregated into six breakout groups, one for each session. The goal of the breakout groups was to discuss current TBI research and identify gaps, barriers, and solutions. The groups also proposed future research topics. Each breakout group was assigned 2-3 specific questions to address. A summary of the group responses for each of the questions assigned is presented below.

Breakout I: Sex Differences in TBI across the Lifespan

How can experts who study sex differences be encouraged to collaborate in TBI research?

Encouragement for collaboration could come about through groups and meetings such as this one as well as small group exchanges. In Canada, each research application has a "sex gender champion" and something similar in the U.S. might be helpful. Providing training on sex differences may help open avenues for collaboration. Also, sex-specific analysis should be made an expectation rather than an afterthought.

Can lifespan questions be better addressed by collaborations between groups currently collecting TBI data? How can collaborations be facilitated?

Researchers suggested expanding the question above so that it reads: "Can lifespan questions be better addressed by collaborations between groups currently collecting *TBI, agent, and aging data*?" In terms of facilitating collaborations, it would help to promote sharing of data or databases for secondary analysis or data mining. Graduate students could work on analyzing those data.

What additional measures need to be included to best address sex differences in natural history studies of TBI?

The following measures were suggested:

- History of injury
- Probing the origin of the injury
- If falls are involved, finding out more about the fall
- Hormones and hormonal disruption
- Utilization of community resources (e.g., rehabilitation)
- Measures of caregiving
- Sex-specific measures

Other items mentioned were the Adverse Childhood Experiences study, accelerated aging, data on “falls” that in reality could be hidden IPV, a history of head injury from any source, trauma, and cumulative trauma.

The group also suggested that the Victims of Crime Act (VOCA) could help pay for rehabilitation costs, which may be helpful to some women. The group emphasized the need to add the patient perspective across the board.

Breakout II: TBI as a Consequence of Intimate Partner Violence

Can research progress on IPV-TBI begin with interrogations of large, ongoing clinical trials, such as TRACK-TBI, AURORA, and CARE?

Based on what is known about those big datasets, the questions that are critical to IPV-related research are not there, thus interrogations would be neither feasible nor possible. Perhaps some questions can be added to someone’s research protocol, but that usually tends to be difficult and might provide only minimal gains.

What research areas and gaps should be prioritized on IPV populations (e.g., natural history studies, cross-sectional studies) and how can researchers control for comorbidities?

Comorbidities can be controlled by assessing the variables that are important with respect to this group and population (e.g., depression, anxiety, childhood abuse, anxiety) as well as potentially other variables that may be involved in the methodology. These can then be added as covariates in the analyses. If one has big enough samples, subsamples of groups could also be examined.

Research areas to be considered include imaging, biomarkers, comorbidities, and the overlap with PTSD and depression. One should study women who have a history of domestic violence and TBI and consider them as a separate population, rather than comparing them to sports-related TBI

populations. In terms of gaps, the whole IPV-TBI subject area could be considered a gap as there is not much information available in the literature.

What types of studies and research strategies are the most valuable and feasible?

Dedicated funding is needed. There are DoD, NIH, and other funding sources for TBI related to sports and the military, but not much funding dedicated to IPV. Since the IPV population is unique, it would not be appropriate to take what has been found in sports or the military research and apply it to IPV. It would also help if both review sections and reviewers would agree that this is an important research area.

Breakout III: Lost in Translation: Sex Differences in Preclinical and Clinical Research

How can we reconcile the translational challenges faced by TBI researchers in both directions (preclinical to clinical; clinical to preclinical)?

Group members explained that animal models tend to be very homogeneous while TBI in humans incorporates a large swath of patients. This can make it difficult to translate animal model findings to the general population.

Another challenge is that the mild, moderate, and severe TBI categories used in humans do not easily translate into the mouse or rat model. For example, a mouse can have a small brain hemorrhage which could be considered mild TBI, whereas in humans a small hemorrhage would never be considered “mild.”

The ability to reproduce studies can be another challenge. Publications often lack the necessary detail to replicate studies. Without these details, it is difficult to determine whether the study’s findings could be built upon or generalized. Access to negative data by researchers could also be helpful as it could help move translation forward more rapidly.

Group members also suggested providing better training on statistics to young investigators, as they have found that some postdocs are poorly trained in statistics.

Two other specific recommendations were made related to biomarkers and data elements. Group members suggested having common data elements for animal studies just as there are common data elements in human studies. In the area of biomarkers, one needs to keep in mind that a functional outcome can also be a biomarker. Unfortunately, biomarkers can at times offer only blunt measures (yes or no, severe or moderate, etc.). A functional outcome should be able to address the nuances of a clinical situation.

What can funding agencies do to enhance translational success, not just financially but also administratively?

One way that funding agencies can help is by supporting multi-center animal trials. NIH could develop cooperative agreements for these trials similar to those already existing for the clinical research networks.

NIH should also clarify what is needed from researchers. Should researchers determine the mechanism before moving forward or should they find out if a product works and *then* find the

mechanism?

Breakout IV: Sex Differences following Sports-Related TBI

What are the high priority knowledge gaps regarding sex differences that currently exist in sports-related TBI?

With respect to high priority knowledge gaps, the group said there was a need for:

- Objective biological measures to assess concussions
- Treatment consistency among providers
- Continued focus on hormones and the need for continued work and research in this area
- Comparative effectiveness research to determine how to treat individuals across the spectrum for mild TBI in sports
- Continued focus on the psychological and psychiatric TBI outcomes among women in sports environments
- A large and comprehensive dataset where women are not just a cohort or a subcohort
- Research that considers various age groups as well as sports that go beyond high school or NCAA, such as extreme sports, action sports, parachuting, etc.
- Considering clinical bias as a variable, depending on the context

The group also suggested that one should avoid a “one-size-fits-all” approach and focus instead on sex and age-appropriate treatment and rehabilitation

What information should be collected in clinical TBI research in order to better interrogate data for sex differences? Is this information being collected by current studies that focus on sports-related concussion?

In smaller studies, one needs to make sure the right controls are in place. One should also consider carrying out exclusive sex-specific studies and momentarily step away from comparison studies. In addition, it’s important to take advantage of already existing large datasets as well as to collaborate by sharing other datasets.

Breakout V: Military Perspective: Sex Differences in TBI among Service Members and Veterans

Does our current knowledge of TBI in men vs. women service members and veterans warrant a differential approach to diagnosis, prognosis, and/or treatment of male vs. female service members and veterans?

One of the concerns that group members voiced is that there currently aren’t enough data to determine differential TBI treatments for female vs. male service members and veterans.

To help address this, health care providers should consider asking appropriate questions and taking an appropriate history and physical that considers TBI and sex differences, such as where the patient is in her menstrual cycle, asking negative vs. positive predictive indicators, determining pre-existing factors, etc. In addition, different disciplines may need to have different criteria for diagnosing and treating patients (e.g., physical therapists, occupational therapists, psychologists, etc.).

Group members stressed a need for education within the military on how men and women respond differently to a concussion (e.g., differences in depression and PTSD in women vs. men).

What information will advance the field toward understanding and addressing differences in the diagnosis, prognosis, and/or treatment of male vs. female service members and veterans?

Group members offered the following suggestions:

- More longitudinal studies involving women
- Better biomarker studies
- More research on better outcome methods or intermediate outcomes (this may involve biomarkers but also needs to involve physical outcome measures)
- Functional outcome measures (e.g., include home and work)
- Widening the outcome measures for female vs. male patients to determine their desired outcome
- Developing female-specific clinics or units in the VA (e.g., the VA could create female-friendly wards or areas for inpatient care)
- Following the model of headache medicine in terms of overall treatment
- Having more sensitive and deployable imaging techniques that help correlate imaging to functional outcomes (e.g., relating imaging to symptoms)
- Better interface between DoD and VA to move EMRs seamlessly between both institutions
- Increased research on oculomotor assessments
- Increased veteran assessment on causes of concussion other than blasts (e.g., falls and sports)
- Developing better coding for TBI
- Developing a clearer definition for TBI
- Developing heightened awareness on the causes of TBI
- Developing a better understanding of who responds best to certain interventions

- More studies on antidepressant efficacy, especially for women with TBI
- Collecting data on lifetime exposure to TBI

Breakout VI: Sex Differences in Diagnosis, Prognosis, and Management of TBI

What information should be included to account for sex differences when different modalities of biomarkers are being developed and analyzed?

Group members said it is important to distinguish between biomarkers and outcomes, particularly in symptoms related to mild TBI. Research should also account for menstrual symptoms, since some menstrual symptoms can be similar to those in mild TBI.

Researchers could also examine biomarker literature in other fields, where sex has been considered a biological variable, such as in Alzheimer's disease or stroke. These models could then be adapted for TBI where one can examine the impact of sex on the performance of biomarkers, as well as other potential effects such as epigenetics, protein expression, etc.

What are the greatest knowledge gaps in sex differences related to the prognosis and management of TBI and how can funders help address those gaps?

In terms of management, a lack of understanding exists on the impact of sex differences on commonly prescribed TBI medications. For example, there are no studies on sex as a biological variable on the use of ibuprofen for mild TBI.

There also are significant gaps in terms of sex differences in TBI rehabilitation, with very few publications noted. Gynecological health and reproductive health for both men and women need to be further explored. For example, what are the effects of TBI on fertility or menopause?

Other outcomes that can be considered are developmental stages since there is a bimodal distribution in the incidence of TBI in early and older age, with a paucity of data on older women with respect to outcomes and management.

With respect to long-term outcomes, there are some concerns related to outcomes measurement in TBI, their lack of precision, and the lack of precision related to women's social roles. For example, one should consider using new economic models that use relative income contribution or the level of cognitive demand for basic tasks as measures instead of "return to work."

Summary and Closing

Walter Koroshetz, MD, Director, National Institute of Neurological Disorders and Stroke, NIH

Dr. Koroshetz thanked all participants and presenters. He once again emphasized the importance of using sex as a biological variable in all NIH research, including TBI research. He provided a brief summary of the items discussed during the conference. Dr. Koroshetz also explained that during the conference presenters discussed studies that clearly showed TBI sex differences in neuron anatomy, neural mechanisms, gonadal hormones, immunity response, and symptoms.