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Understanding Traumatic Brain Injury in Females: A State-of-the-Art Summary and Future Directions

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Abstract

In this report, we identify existing issues and challenges related to research on traumatic brain injury (TBI) in females and provide future directions for research. In 2017, the National Institutes of Health, in partnership with the Center for Neuroscience and Regenerative Medicine and the Defense and Veterans Brain Injury Center, hosted a workshop that focused on the unique challenges facing researchers, clinicians, patients, and other stakeholders regarding TBI in women. The goal of this "Understanding TBI in Women" workshop was to bring together researchers and clinicians to identify knowledge gaps, best practices, and target populations in research on females and/or sex differences within the field of TBI. The workshop, and the current literature, clearly highlighted that females have been underrepresented in TBI studies and clinical trials and have often been excluded (or ovariectomized) in preclinical studies. Such an absence in research on females has led to an incomplete, and perhaps inaccurate, understanding of TBI in females. The presentations and discussions centered on the existing knowledge regarding sex differences in TBI research and how these differences could be incorporated in preclinical and clinical efforts going forward. Now, a little over 2 years later, we summarize the issues and state of the science that emerged from the "Understanding TBI in Women" workshop while incorporating updates where they exist. Overall, despite some progress, there remains an abundance of research focused on males and relatively little explicitly on females.

Keywords

concussion; intimate partner violence; sex differences; traumatic brain injury; women

TRAUMATIC BRAIN INJURY (TBI) is a common and often devastating injury affecting all sexes and genders. However, much of what is known about TBI comes from preclinical

and clinical studies of male subjects, leaving large gaps in the understanding of females and sex- or gender-related differences in epidemiology, prevention, neuroprotection, secondary injury, rehabilitation timing and therapeutics, and specific outcomes. The prediction that meaningful sex differences exist in TBI is based on the vast body of literature demonstrating important sex differences in whole-brain and regional measures of brain anatomy and function in the healthy brain[1,2] as well as sex differences in civilian TBI.[3,4] Sex-related differences in outcomes appear to depend on a range of factors including how and what is studied; for example, a recent review[5] concluded that females have worse outcomes than males when studying humans but better outcomes than males when studying animals. Variables such as sample size, study design, and severity of TBI also affected whether females fared “better” or “worse” than males. It is vital to address the effect of sex and gender on all aspects of TBI across the life span to produce better scientific knowledge and clinical care for women and girls. It is also important to study populations for which females are more likely to be at a higher risk than males to experience a TBI, as is the case for intimate partner violence (IPV).

The National Institutes of Health (NIH) refers to sex as the biological and physiological characteristics that distinguish male bodies from female bodies (eg, anatomy, physiology, genes, and hormones). Gender is described as a social construct that is culturally based and historically specific (eg, “feminine” identities, behavioral norms, and expectations).[6] We refer to sex and gender binarily, reflecting the current literature, but recognize that they are fluid constructs. Figure 1 illustrates the range of factors that may contribute to outcomes in TBI research with sex (and gender) playing prominent roles.[7]

RATES AND OUTCOMES OF TBIS DIFFER BY SEX ACROSS THE LIFE SPAN

Issue:

The variation in the leading causes of TBI throughout the life span and across the sexes.

Challenge:

Predominant causes of brain injury (BI) vary on the basis of age and sex, creating a complex landscape for researchers and clinicians who seek to identify the natural history, risk factors, and potential treatments of TBI.

Epidemiologic analyses have typically shown a higher overall rate of TBIs, based on *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic codes, in males than in females.[8] For example, in 2013, males had higher rates of TBI-related emergency department visits, hospitalizations, and deaths (EDHDs) due to the following: being struck by or against an object; motor vehicle crashes; intentional self-harm; and assault.[8] However, females had a higher number and rate of TBI-related EDHD as a result of falls, with most TBI-related EDHD due to falls sustained by older adults. Here, we present epidemiologic data for both pediatric and aging populations. This is important as TBI incidence peaks in both early childhood and late adulthood.

Pediatric populations—The literature on sex differences in pediatric TBI is summarized in a recent review,[9] which describes the origins of sex differences and the convergence of sex differences with developmental BI pathobiology. Overall, across all pediatric age ranges (0-17 years), young females have a lower incidence of TBI than young males, with young males aged 0 to 4 years having the highest incidence rates.[10] In general, young males are about 2 times more likely than young females to have a TBI.[10,11] A number of factors have been identified that may contribute to the sex differences in epidemiology of TBI such as a higher incidence of general injury among younger males, variance between males and females in traditional societal roles and activities, as well as differences in risk-taking behaviors. In addition to incidence rates, there appear to be important sex-based differences in outcomes after pediatric TBI. A large database study using the National Pediatric Trauma Registry evaluated patients aged 0 to 19 years and subdivided them by age into prepubertal (0-7 years), indeterminate pubertal (8-12 years), and probable pubertal (13-19 years). This study indicated that the overall (all ages) mortality rate, hospital length of stay (LOS), and overall functional outcomes were not different between young males and females with TBI.[12] However, young females did have a longer intensive care unit (ICU) LOS than males and trend toward worse outcomes. More specifically, adolescent females (aged 13-19 years) had longer hospital and ICU LOS, with a greater likelihood of needing rehabilitation. In another large database study, investigators used the National Trauma Data Bank from 2007 to 2008 to calculate sex differences in mortality rates after TBI, before and after puberty. In a cohort of 20 280 patients, with approximately 50% prepubescent and approximately 50% pubescent, there were no sex differences in mortality rates in prepubescent patients; however, female sex was associated with reduced mortality in the pubescent cohort.[13]
A few limited studies that focused on sex differences in cognitive outcomes following TBI suggest that young females perform better than males on postinjury testing.[14,15] For example, in 2 separate investigations, Donders and colleagues[16,17] studied children aged 6 to 16 years, consecutively referred to their rehabilitation center following TBI, over a 4-year period. Within their study population in both sexes, approximately 50% were classified as mild-moderate TBI and approximately 50% were classified as severe TBI. They found that young males with TBI performed worse than young females with TBI and healthy age- and sex-matched controls on learning, retrieval, and processing speed. A longitudinal study in New Zealand (BIONIC) evaluated cognitive and behavioral outcomes in children (aged 2-15 years) after mild TBI and showed worse generalized cognitive function in males at 1 year after injury.[16] In contrast, at 4 years after injury, there were no sex differences in overall neurocognitive outcomes, but female sex was associated with worse social quality-of-life scores.[17] In addition, a recent study evaluated sex differences in psychosocial functioning in adulthood (18-31 years; >5 years since injury) following childhood TBI (0-17 years).[18] They included all severities of childhood TBI and categorized them as mild and moderate/severe. Across all severities of TBI, they found that females were significantly more likely than males to report internalizing problems, such as depression and anxiety, while males were significantly more likely to report externalizing problems, such as substance abuse or criminal behavior. Another study in 210 children with TBI revealed that male sex (hazard ratio = 1.97; 95% CI, 1.03-3.77) was associated with an increased risk for attention-deficit/hyperactivity disorder secondary to the TBI, defined as T-scores higher than 65 on the *DSM*-Oriented Attention-Deficit/Hyperactivity Problems Scale on the Child-Behavior Checklist.[21]

Taken together, these studies suggest that sex and/or gender play a role in cognitive and psychosocial outcomes after pediatric TBI.

Previous studies have found that adolescent concussion rates are higher among females than among males in sex-matched sports.[20,21] Using the High School Reporting Information Online surveillance system of more than 6000 adolescent sports-related concussions (SRCs), one study found that girls' soccer had the highest rate of concussions versus any other sex-matched sport in 2014-2015.[20] In another study of adolescent SRCs, investigators found that aggregate concussive symptoms were higher in female athletes than in males, both at baseline and immediately after injury.[22] However, the trajectory of recovery was similar between males and females. This would suggest that understanding the baseline level of symptom frequency is important for assessing recovery of female athletes after concussion. A recent systematic review of concussion in student athletes concluded that females generally take longer to recover after concussion, although there are mixed reports on sex differences in recovery times and persistent symptoms.[23] The authors highlighted that factors such as injury biomechanics, injury rates, and frequency of symptom reporting in females might account for these differences.

In summary, clinical studies in children have demonstrated sex differences in functional outcome, ICU LOS, and mortality after pediatric TBI. In addition, potential sex differences were found in pediatric and adolescent concussions, with a longer recovery time in female athletes but with a higher baseline rate of symptom reporting. These sex-based differences in adolescents could be influenced by systemic sex hormone differences and/or gender. However, clinical and preclinical studies have shown sex-based differences even prior to puberty. In conclusion, in future studies, it is important to separately evaluate male and female subjects in studies of pediatric TBI. Failure to consider sex as a biological variable could restrict translatability of preclinical therapies and limit the value of clinical research in pediatric TBI.

Aging populations—The epidemiologic profile of TBI indicates that rates of TBI *hospitalizations* by sex are similar in older adulthood, which contrasts with younger age groups where males are disproportionately represented.[24] Yet, females 65 years and older have been found to have the highest *rates* for diagnosed mild TBI.[25] Falls are the major cause of injury, particularly among females.[24] Furthermore, females have been found to represent the majority of Medicare and home care patients with TBI in the older adult population.[25-28] Aging with TBI was identified as a priority area at the first international workshop on women and TBI in 2010.[29] Despite this focus at conferences, no systematic reviews on older adults with TBI have given explicit consideration to sex. Therefore, there is limited knowledge to inform sex-specific interventions and guidelines.[30-33] Older adults have been found to make similar gains in inpatient rehabilitation settings as younger adults[34] and as such sex and gender information is needed to inform best practices for older TBI patients, which currently are lacking.

In a study of 306 former inpatient rehabilitation patients aging with TBI up to 24 years postinjury, women reported more headaches and dizziness as well as increased loss of confidence compared with men.[35] The symptoms more likely to affect daily functioning

among women reported were the ability to initiate daily activities, high sex drive, and a need for supervision and assistance. These identified problem areas reflect gendered roles, indicating that being cared for was more problematic for women likely due to reversed major caregiving roles. Although men were twice as likely to report high sex drive, women considered this symptom to be more problematic. Subsequent work from focus groups of survivors with more moderate to severe injury and caregivers revealed the increased potential for sexual abuse among women after BI.[36] In terms of large population studies, older females have been more likely to be institutionalized after hospitalization for TBI after controlling for age, injury severity, comorbidities, and mechanisms of injury.[37] Long-term outcome studies are important as they have identified specific service needs for women aging with TBI.[38]

Population-based studies have also shown that more male and female older adults hospitalized with a TBI diagnosis experience multiple co-occurring comorbidities post-TBI, as well as higher mortality rates, compared with younger individuals. The most frequent comorbidities associated with hospitalizations following TBI related to circulatory system difficulties.[24] In the inpatient rehabilitation setting, older females were significantly more likely than older men to have a musculoskeletal comorbidity, including diagnoses such as osteoporosis and arthritis, as well as mental health diagnoses.[39] Furthermore, a recent study of more than 90 000 individuals with a concussion[40] found that neck injury comorbidity was significantly higher in females, with the highest rates between the onset of puberty and the onset of menopause. Rates of comorbid neck injury were similar between sexes in older adulthood, with non-linear trends with respect to age and this comorbidity. A large study of more than 700 000 persons hospitalized with a TBI diagnosis followed over time showed that the risk of dementia increased with comorbid spinal cord injury, with females at a higher risk of an earlier onset of dementia.[41] Notably, other data showed that a higher number of comorbidities were more likely to impact functional outcomes for males than for females in the rehabilitation context.[42]

Other sex-specific analyses have identified different predictors of post–mild TBI pain by sex.[43] Overall, these data speak to the importance of examining comorbidities in understanding potential sex-related differences in outcomes from TBI.

Suggestion:

Clinical research suggests important sex-related differences in responses to injury and treatment. The following actions may advance research on sex differences in TBI across the life span.

1. In studies of TBI across the life span, include an evaluation/analysis separately by sex.
2. Investigate sex-specific as well as sex-related differences and similarities in responses to injury in terms of differential patterning rather than dichotomous worse/better outcomes and include longer-term outcomes.
3. Consider hormonal and pubertal status as variables in TBI outcome research.

MOST DATA ON TBI "GROUPS" HAVE FOCUSED ON MALES

Intimate partner violence (IPV)

Issue: Lack of data aimed at understanding the prevalence and effects of IPV-related BI

Challenge: Despite decades of evidence that single and repetitive BIs are a common consequence of IPV, there has been very limited research addressing outcomes from these injuries, including the potential role of BI-related cognitive impairments that may serve as an additional barrier to escaping violent situations. The limited research that has been conducted suggests that women are sustaining repetitive BIs from their partners at high rates and that these BIs contribute to a host of cognitive, psychological, and behavioral problems as well as impairments in functional and structural neural connectivity.

IPV is one cause of BI for which women are more vulnerable. Nationally representative studies of IPV have shown a higher prevalence among women than among men, particularly for the more severe forms of IPV that are more likely to cause a BI.[44] For this reason, and also because IPV-related BI in men has not been previously studied, this discussion on IPV-related BIs focuses on women.

Women subjected to IPV sustain a range of traumas to the head that have the potential to cause TBI. Women are hit on the head with fists and other hard objects, have their heads slammed against walls and floors or kicked with boots, are thrown downstairs, and are violently shaken.[45] In addition, women are strangled–sometimes into unconsciousness–resulting in acquired brain injuries from ischemic and hypoxic insults to the brain.[45-47] Not surprisingly, a number of reports have indicated that up to 94% of injuries women sustain from abuse are to the neck and higher.[48,49]

Unfortunately, good epidemiologic data regarding the prevalence of IPV-related BIs are sorely lacking. One nationally representative study found that 14.6% of women who experienced sexual violence, physical violence, or stalking by an intimate partner in their lifetime had been "*knocked out* after getting hit, slammed against something, or choked."[50] This represents 6.2 million women who have experienced loss of consciousness (LOC) from an intimate partner. This number does not even include any BIs that may have presented with other indicators of BI such as confusion, disorientation, or amnesia. Other studies, though not epidemiologic in nature, have included these other indicators and have suggested much higher rates (eg, 35%-74%) of IPV-related BIs.[51-54]

The earliest studies to address this issue were in the late 1990s/early 2000s.[52-54] These studies provided initial estimates of IPV-related BIs as well as psychological and cognitive correlates. First, Monahan and O'Leary[54] found that 35% of women residing in a shelter experienced a head injury from their partner, with 44% of these women reporting LOC; these women were also more likely to endorse somatic, cognitive, and emotional symptoms than women without a history of head injury. In a sample of 53 women who had experienced IPV, Jackson and colleagues[52] found that 92% reported some type of blow to the head and 40% reported LOC after being hit on the head or severely shaken. A majority of women with LOC reported postconcussive symptoms (PCSs), with a dose-dependent response

between the number of repetitive BIs and cognitive symptoms (eg, easily distracted, trouble concentrating). Finally, in a sample of women who had experienced at least one instance of physical partner violence, Valera and Berenbaum[53] found that 74% sustained at least one IPV-related BI and 51% had a history of repetitive BIs. Furthermore, BI scores were negatively associated with measures of learning, memory, and cognitive flexibility (eg, the higher the BI score, the more difficulty a woman had learning and later remembering a list of words) and positively associated with measures of general distress, depression, anxiety, worry, and posttraumatic stress symptoms. Importantly, these associations remained after controlling for the effects of abuse severity, suggesting that the BIs, rather than the severity of the partner abuse itself, accounted for these associations. Furthermore, as a majority of the women were tested at least 3 months after their most recent BI (unpublished data), the data suggest that these could be persistent, if not permanent, effects. All of these data clearly indicated that a better approximation of the prevalence of IPV-related BIs among the general population is urgently needed.

Since that time, a slowly growing number of reviews have focused on summarizing the scope and importance of understanding IPV-related BIs in women,[51,55-58] including the recent publication of 2 special issues on this topic in the *Journal of Aggression, Maltreatment & Trauma*.[59,60] Outside of reviews, data studies providing specific information about the correlates and effects of IPV-related BIs are rather scarce, although they are growing in number. Overall, these studies of community, shelter, and veteran samples reveal a host of negative outcomes associated with IPV-related BIs (or "probable TBIs"). In one study, women visiting primary care and family planning clinics were surveyed.[47] Among women who had been abused, those who had experienced a "probable TBI" were significantly more likely than those who had not experienced a probable TBI to report a greater number of "central nervous system (CNS) symptoms." These symptoms included blacking out, dizzy spells, and ears ringing, as well as problems with memory, concentration, vision, and hearing. This observation is notable in that women were not recruited on the basis of abuse or TBI history but were merely visiting primary care and family planning clinics. In a more recent study on Black women with a history of abuse, approximately one-third of women had a probable IPV-related BI.[61] Presence of a probable BI was associated with an increased risk of depression, posttraumatic stress disorder (PTSD), and physical injuries compared with women without a probable BI history. Furthermore, a survey study of women veterans reported higher levels of depression and PTSD symptoms, as well as poorer perceived physical health, in those with an IPV-related BI history than in women without a BI history.[62] In addition, relative to women with no IPV-related BI history, women with IPV-related BI with ongoing symptoms were reported to be nearly 6 times as likely to experience probable IPV-related PTSD.[63] Notably, all women veterans who were surveyed experienced IPV, suggesting that this effect was related to BI, rather than the IPV itself, similar to what was observed in a prior investigation of civilians.[53] Finally, in a recent study that evaluated women survivors of IPV, Smirl and colleagues[64] found that an IPV-related BI score (as was used in the Valera and Berenbaum[53] study) was associated with a greater degree of depression, anxiety, and symptoms related to arousal and memory/cognition. Symptoms such as "fatigue or low energy," "nervous or anxious," and "dizziness" were most strongly associated with the TBI score and were

recommended for use in future screening. Overall, these studies demonstrate the relationship between IPV-related BIs and a host of negative emotional, somatic, behavioral, and physical outcomes for women experiencing IPV.

Despite the hundreds of neuroimaging studies examining the effects of TBI on military veterans and athletes that largely comprise males, there are currently only 2 such studies examining the effects of IPV-related BIs. These studies examined associations between IPV-related BIs (including from nonfatal strangulation) and functional and structural neural connectivity.[45,65] The initial investigation showed a negative correlation between a BI score and default-salience internetwork connectivity.[45] In addition, there was a significant correlation of positive connectivity among these networks with a woman's ability to learn and remember a list of words. The subsequent study provided evidence for a negative relationship between this same BI score and measures of fractional anisotropy in 2 of the 3 hypothesized regions of interest, namely, the posterior and superior corona radiata.[65] Importantly, none of the aforementioned relationships could be accounted for by abuse severity or other potential confounds (eg, drug abuse, child abuse, psychotropic medications). This research provides preliminary evidence that an IPV-related BI is deleterious to women's neural and cognitive health. As these are the only imaging studies to date to address this issue, additional work is desperately needed.

Suggestion: Initial estimates suggest that women sustain high rates of BIs at the hands of their intimate partners. A greater awareness of IPV-related BIs and their effects is critically needed in order to more effectively interact with, intervene, and treat women who have experienced an IPV. The following activities and focus areas would facilitate this effort:

1. Obtain representative prevalence estimates of single and repetitive IPV-related TBIs and/or strangulation related BIs in the general population.
2. Examine the biopsychosocial effects of IPV-related BIs by simultaneously assessing neural, cognitive, psychological, and social functioning as well as perceived needs among these women.
3. Develop objective biomarkers for the diagnosis, prognosis, and historical assessment of IPV-related BIs. These markers must account for sex-specific variability, as well as comorbidities including other potential trauma.
4. Understand the role of IPV-related BIs in relation to the risk for chronic BI-related symptoms, progression of chronic neurological disorders, and dementia. This should include development of clinical assessment and biomarkers appropriate for this population.

Sports

Issue: Lack of understanding of sex differences in the effects of sports-related concussion (SRC) across development and into early adulthood

Challenge: Research on SRCs has focused on a relatively narrow age range of adolescent and young adult student athletes, with only sparse representation of young/early adult female and male athletes. In addition, long-term follow-up data are lacking in most studies of SRCs

in student athletes; researchers focused on specific levels of the education system may lose track of athletes after graduation.

Previous research has found sex-related differences in outcomes following SRC.[66] Major findings from investigations that focused on sex differences include a higher rate of SRCs in females in sports common to both female and male athletes; for example, in soccer and water polo.[67-69] High school studies have also reported a higher incidence of SRC in female athletes.[68] Research evaluating the time for symptom resolution and clearance by clinical providers for return to play include multicenter epidemiologic projects on SRC or mild TBI of various causes and clinic-based investigations at a single site.[23,67,70] Most studies have found that PCSs are more severe and/or slower to resolve after injury in females than in males.[23,67,70,71] In fact, female sex was identified as a risk factor for prolonged recovery of PCSs in a multisite emergency department (ED) study of pediatric concussion.[70] This sex difference also applies to studies that have compared the proportion of female and male athletes whose recovery extended longer than 1 month.[67] In addition, sex-specific effects have been reported for specific types of PCSs; posttraumatic headaches were more common in female than in male athletes as was a history of preinjury migraine.[72] Vestibular dysfunction was more persistent in female athletes in a study that used the Vestibular Oculomotor Screening test,[73] but Ozinga and colleagues[74] found that the direction of sex differences in performance on the Balance Error Scoring System depended on whether the athletes were in high school or college.

The evidence for sex-specific effects is less consistent for cognitive deficits after SRC. Visual memory and visual motor speed, as measured by the ImPACT, have been shown to be more severely impaired during the subacute phase of SRC in female than in male athletes.[75,76] In contrast, sex differences have not been reported for concussed student athletes on the Verbal Memory Composite of ImPACT,[75] and other studies have not confirmed the Majerske et al[76] finding. This putative, material-specific visual memory impairment in females after SRC may be attributable, in part, to sex differences in visual versus verbal memory in the general population, since evidence supports a male advantage in visuospatial processing and better verbal memory in females.[77] Although these sex differences have not been widely confirmed by SRC studies using the ImPACT Verbal and Visual Memory Composites, the format of these subtests may not be conducive to demonstrating differences in performance between male and female athletes.

SRC investigators have seldom used a developmental perspective in their interpretation of cognitive differences between concussed female and male athletes. The sex difference in the chronobiology of brain maturation has also not been considered in SRC studies. One developmental study of the brain connectome in the 8- to 22-year age range found that the trajectory of connections during the adolescent to adult transition was sexually dimorphic; male connectivity emphasized intrahemispheric connections, whereas female connectivity was more interhemispheric.[78] This dimorphism was interpreted as facilitating coordination between perception and action in males and integration of analytic skills with intuitive abilities in females. The relation of these divergent trajectories of connectivity to recovery from concussion awaits further research. Although computerized batteries of tests have greatly facilitated enrolling large samples of student athletes, the range of memory tasks

is quite limited and may fail to detect subtle SRC effects that are apparent under specific conditions such as a long delay or by varying the test materials to accentuate interference, organizational strategies, or visuospatial processing.

Several hypotheses have been advanced to explain sex-specific effects of SRC, including more robust axonal infrastructure in males as reported in a rodent model,[79] sex differences in cerebral blood flow,[80] variability in level of steroid hormones associated with the menstrual cycle and affected by concussion,[81] and stronger, larger necks in males,[82] and more open disclosure of PCSs by female than by male athletes.[70] In one study exploring sex differences related to disclosure, Sanderson and colleagues[83] surveyed a sample of male and female athletes to investigate their experiences with concussion reporting. They found that male athletes were more likely to not report a concussion due to team allegiance whereas female athletes were more likely to not report based on the "pain principle,"[84] an ideological belief that athletes must play through pain to be valued. In addition, female athletes were more likely to not report a concussion because they did not perceive their injury as severe. Structural barriers, such as lack of resources (eg, not having an athletic trainer present), were also related to nonreporting, with females being more likely to not report due to lack of resources than males. These results suggest that concussion management needs to include discussion around sport cultural values, such as violence and playing through pain, and access to resources, as these factors impact both male and female athletes.[85,86]

It is certainly plausible that multiple mechanisms are involved or that other explanations will emerge from neuroscience, biomechanics, or other domains of research. Advances in brain imaging may enhance identification of sex differences in white matter tract characteristics, and improved remote sensors to detect head acceleration may facilitate more rigorous investigation of sex differences in neck musculature. Psychophysical approaches to studying sex differences in response to controlled sensory input under laboratory conditions may mimic symptoms of dizziness, photosensitivity, or noise intolerance and inform the underpinnings of persistent PCSs in female athletes.

Suggestion: Research emphasis in the following areas would advance our understanding of sex-related differences regarding the risk factors, causes, and sequelae of SRC:

1. SRC research focused on pre–high school and postcollegiate athletes to evaluate the effects of hormonal change across the life span in both male and female athletes.
2. Clear definitions, methods, and measures of assessing exposure acutely, longitudinally, and historically, with particular attention to high female participation sports. For example, improved head impact and accelerometer data for female dominated, nonhelmeted sports.
3. Linkage of data from EDs, pediatricians, and concussion clinics with surveillance programs would allow for more accurate evaluation of the total BI exposure experienced by male and female children and adolescents who participate in sports.

4. Investigation of sex-specific differences throughout brain maturation and at long-term recovery points after SRC.

Military service

Issue: Limited understanding of the effect of military-related TBI exposure on female veterans and military personnel

Challenge: An increasing number of women are serving in the US Army, Air Force, Navy, and Marine Corps, with 18.5% of officers and 16.7% of personnel being composed of women as of January 2020.[87] In 2015, it was announced that women would be allowed to serve in all military positions, including combat roles.[88] Despite the increasing involvement of females in the military and in combat roles, most TBI research studies in this population exclude women or include a small number of female participants. This trend has resulted in a dearth of evidence with regard to potential sex differences in incidence, outcome, and recovery of military TBI. Furthermore, the potential role of sex in the neurobiological correlates of military TBI needs more investigation. In addition, the few observational studies (summarized later) that included sizeable numbers of female participants have demonstrated that sex may be an important predictor of TBI outcomes in the military and veteran populations.

Data from studies that have included both sexes support the concern that we may be missing important information when excluding female participants and suggest that results based only on male participants may not be a generalizable. For example, a study by Iverson and colleagues[89] examined the impact of sex on psychiatric comorbidities and self-reported PCSs in 12 605 veterans with a history of TBI (5.2% female). After controlling for blast exposure, women were significantly more likely to have depression, depression comorbid with PTSD, alcohol use disorder, and a higher number of self-reported PCSs.[89] These results are consistent with findings from a number of studies showing greater levels of symptom reporting among women than among men[90-92] but in contrast to several other investigations that did not observe a significant effect of sex on post-TBI symptom reporting.[93,94] Furthermore, sex-based differences were attenuated after controlling for PTSD and symptom validity,[92] suggesting that it may be necessary to account for these factors when evaluating the effects of TBI in military populations. In addition, female veterans with TBI experience a wide range of nonspecific symptoms such as nausea, fatigue, appetite changes, and sleep distrubances.[91] For reasons not clearly known, these symptoms seem to be less frequently reported by male veterans with mild or moderate TBI. Female veterans were also more likely to report headache and depression following TBI, whereas male veterans are more likely to report low back pain after the injury.[95] A recent study comparing male and female veterans with mild TBI (matched with respect to age, time since injury, and mechanism of injury) showed a significant effect of sex on the Neurobehavioral Symptom Inventory composite cognitive domain factor, with male veterans showing a significantly higher score than female veterans.[96] Taken together, these studies suggest that as in civilian samples, TBI symptoms varies by sex among Veterans.

The existing studies examining sex differences in military TBI are predominantly observational and cross-sectional, limiting what is known about sex differences in long-term outcomes of military TBI. Moreover, much of the data are potentially biased by examining outcomes only from individuals who receive Veterans Affairs care. Apart from the benefit of identifying causal factors, longitudinal data also provide an opportunity to observe the evolution of comorbid conditions. For example, studies examining longitudinal comorbidity phenotypes in a sample of post-9/11 veterans have reported similar phenotypes for men and women. However, a recent latent class analysis stratified by sex (144 717 males and 20 216 females) suggests that, while there are more similarities than differences in TBI-related comorbidity phenotypes, there are also meaningful differences by sex. Of particular interest, a pattern in men that demonstrated improvement (reductions in care for mental health, pain, headache, cognitive complaints) over 5 years was not found for women. Rather, a pattern of pain and depression was revealed for women (M. Pugh et al, unpublished observations).[97] This strategic approach to examining outcomes after TBI or PCS may benefit from collection of neuroimaging and longitudinal biomarker data to better understand the evolution of phenotypes among individuals with similar exposures. However, none of the longitudinal observational studies have included acute injury characteristics and prior mental health and TBI history; thus, the evidence available to examine the issue of sex differences in military related TBI is weak.

Sex differences in resting state functional connectivity have been observed in veterans with TBI. In a study examining orbitofrontal connectivity, females demonstrated more unilateral and focal connections than males whereas males showed more diffuse and bilateral connections than females.[98] In addition, functional connectivity in male veterans with TBI was associated with aggression, a finding not observed in female veterans.[98] These studies highlight specific brain regions and circuits that may be associated with sex differences related to TBI; however, it is unclear whether these neurobiological differences predated the onset of injury or would vary with course of recovery.

Suggestion: Adopting the following strategies may help enhance our understanding of sex differences in outcomes and neurobiological underpinnings of military TBI, which would inform prevention and targeted treatment, and improve TBI outcomes in female veterans.

1. Inclusion of higher numbers of female veterans and military personnel in TBI studies would increase understanding and generalizability of study conclusions.
2. Registry for increasing the availability of female veteran brain tissue for neuropathological assessment of TBI exposure.
3. Assessment of sex differences in preclinical blast models of TBI.
4. Studies that pair observational outcomes (eg, evolution and resolution of PCSs and psychiatric comorbidities) with acute injury characteristics, prior mental health and TBI history, and targeted biomarker and neuroimaging endpoints would increase an understanding of the diversity in outcomes and related neurobiological changes in military personnel over time.

5. Observational studies oversampling females in diverse military occupations would augment an understanding not only of exposures but also the potential for differential long-term impacts by sex.

SEX-SPECIFIC BIOLOGICAL AND SOCIAL FACTORS AFFECT TBI RATES AND RECOVERY

Issue:

Lack of understanding of mechanisms of sex- and gender-related differences in the response to and recovery from TBI.

Challenge:

Most clinical and preclinical TBI research has been conducted in exclusively male populations, leading to an incomplete understanding of the biologic response to and recovery from TBI. The dynamic hormonal milieu of female populations further complicates assessments of sex-based differences.

The observed difference in post-TBI outcomes between males and females may be due, in part, to sex-based variation in the magnitude of and response to BI. The establishment of objective markers of injury and recovery is a first vital step in understanding sex- and gender-based differences in outcomes after TBI. Current clinical management strategies rely heavily on subjective symptom reporting, especially in the case of mild TBI. It remains unclear whether sex-based differences in symptom reporting are based on variations in physiology or also, in part, reflect psychosocial factors related to gender constructs. In mild TBI, PCS scores of females exceed those of males beginning around menarche, peak during the childbearing years, and then return to the level of males after menopause, suggesting a biologic basis of sex differences.[99] However, multiple factors may play a part in sex- and gender-based symptom reporting including innate differences in somatic and visceral perceptions, differences in symptom labeling and/or reporting, differences in socialization and the willingness to disclose discomfort, differences in underlying psychiatric conditions such as anxiety associated with symptom reporting, and research bias in assessment of symptoms. Nonetheless, understanding the complex basis of sex- and gender-related differences in symptom reporting could result in more precise diagnostic criteria and targeted treatments.[100] This is especially important in mild TBI, where symptom reports serve as diagnostic criteria for injury, predictors of outcome after injury, and the outcome itself.

In addition to offering objective markers of injury and recovery, fluid biomarkers may provide some insight into pathophysiological mechanisms underlying sex-based differences after TBI. Differences in both the anatomic and biochemical milieus of the CNS in women compared with men could lead to differences in circulating biomarkers after injury. Animal models suggest sex differences in tissue expression of markers of injury and recovery, though the majority of preclinical TBI studies have exclusively used male animals.[101-103] Similarly, few previous clinical studies have investigated sex-based differences in TBI biomarkers.

Sex-based differences in neuroinflammatory response would be a helpful focus of investigation as well. Acute focal TBI triggers a neuroinflammatory cascade with infiltration of macrophages, activation of endogenous microglia, and release of both pro- and anti-inflammatory cytokines.[104] Neuroinflammation serves 2 contrasting functions after acute injury: to remove damaged tissue and to aid in recovery. If the balance is tipped too far toward proinflammatory factors in the injured brain, there will be more neurotoxicity than neuroprotection.[105] Most TBI studies of neuroinflammation have either been focused upon one sex[106] or not been adequately designed and powered to address sex differences. Of the immune cells known to be involved in the response to acute neurological injury, sex differences have been documented in the responses of macrophages and microglia.[107] Microglial sex differences could become maladaptive during disease states and underlie some of the sex differences in autoimmune disorders, chronic pain conditions, and neurodegenerative diseases.

A preclinical study specifically designed to assess sex differences in neuroinflammation demonstrated that invasion of peripheral macrophages was greater, microgliosis peaked earlier, and lesion volumes within 1 week of moderate-severe TBI were larger in male than in female mice.[108] However, by 30 days postinjury, lesion volumes were similar between the sexes. Endogenous sex steroids may be partly responsible for sex differences in preclinical models of TBI, as seen in another study that found that gonadally intact female mice had less neuroinflammation (both microgliosis and astrogliosis) and better functional outcomes than male mice and ovariectomized female mice after controlled cortical impact.[109] The anti-inflammatory agent minocycline, which was neuroprotective in a mild blast injury model of TBI in a single sex study of male rats,[110] revealed sex differences in posttraumatic thermal, stress, and inflammatory responses between male and ovariectomized female rats in a focal contusion model.[111] A factor that further complicates clinical TBI, adding a caveat to the interpretation of findings from any single preclinical model of TBI, is that the patterns of neuroinflammation may vary depending upon the type of injury. For instance, in a focal contusion model of TBI microglial activation peaked by 1 week,[104] but in a diffuse injury model this microglial activation did not peak until 24 days after injury.[112]

Current in vivo clinical tools to investigate neuroinflammatory responses and sex differences after TBI are limited, with some ability to assess inflammation via magnetic resonance imaging (MRI) (post–gadolinium-based contrast agent scans that can show blood-brain barrier disruption), magnetic resonance spectroscopy, and positron emission tomography with ligands that target markers of neuroinflammation[113] and have not yet been applied to the investigation of sex differences in TBI. A caveat of these neuroimaging approaches is that in most cases, the underlying neuropathology has not been directly correlated with the in vivo imaging findings. Correlation of in vivo/ex vivo MRI findings and neuropathology was performed in the rat for diffusion tensor imaging,[114] but this method is not sensitive to specific types of neuroinflammation, only to the disruption of axonal pathways. While an in vivo MRI with ex vivo histology study in a rat focal contusion model did not observe sex differences in lesion size or microglial activation, sex differences in the cerebrovascular response were observed, with greater numbers and complexity of vessels observed in males than in females at 1 week after injury.[115] PET ligands for translocator protein (TSPO), which is overexpressed in activated microglial cells, revealed sex-based differences in

microglial response in ex vivo binding assays in an investigation of the interaction of age and sex in the neuroinflammatory response in mice after lipopolysaccharide challenge.[116] The application of these ligands to TBI studies of sex differences through in vivo PET investigations has not yet been reported.

Sex differences in the hormonal milieu during recovery have potential to influence the reporting of the PCSs used to determine recovery. Phase of the menstrual cycle has been hypothesized to have an impact on outcome following TBI. Physiological studies of sex differences in TBI-related cerebral edema, cerebral blood flow, and survival have shown conflicting results in preclinical and clinical studies.[23,117-119] However, most symptom-based studies in humans indicate that women have poor outcomes after TBI, especially after mild TBI.[120-122] The observation that worse outcomes for women were most pronounced during childbearing years[99] suggested a role for sex hormones such as estrogen or progesterone. Across the life span, the sexes have similarly low levels of these hormones except during the childbearing years when women have high levels. Both female sex hormones, but especially progesterone, are neuroactive, modulating mood and cognition. In fact, progesterone has been investigated as a possible treatment of TBI.[123,124] But if progesterone is beneficial and perhaps even neuroprotective, why would women of childbearing age have worse outcome than their male counterparts?

The answer may lie in progesterone's wide monthly swing, which is experienced by women, but not men. Progesterone levels are very low during the first 2 weeks of the menstrual cycle (follicular phase) but then rise during the second 2 weeks of the cycle (luteal phase). At the end of the luteal phase, progesterone levels drop rapidly. During this rapid drop, women experience a constellation of "premenstrual symptoms," followed by menstruation. Premenstrual symptoms are thought to represent a type of withdrawal due to a rapid drop in this mood-soothing, cognition-enhancing hormone. The remarkable similarity between premenstrual and PCSs suggested that concussion may also disrupt progesterone production. Support for this theory came from prior studies showing suppression of the function of the pituitary gland–which controls the menstrual cycle–following TBI[125,126] along with studies demonstrating missed or abnormal menstrual periods after concussion.[127]

To test this theory, researchers examined a group of 144 women of childbearing age (16-60 years) presenting to an ED within 4 hours of mild TBI. Women were classified into menstrual cycle phase by serum progesterone concentration and self-reported contraceptive use (which provide constant high levels of synthetic progestins). One month after injury, their PCSs and quality of life were measured. Women injured during the luteal phase of their menstrual cycle, when progesterone concentration was high, had significantly lower quality of life and more PCSs than women injured during the follicular phase or women taking oral contraceptives. Multivariate analysis confirmed a significant independent effect of menstrual cycle phase on quality of life and PCSs. Interestingly, women with high levels of progesterone during and after the injury due to synthetic progestin (birth control) had outcomes that were no different from those who were in the follicular phase of their menstrual cycle.[81]

These results support a “withdrawal hypothesis” to explain sex differences in outcomes after mild TBI. Mild TBI occurring in the setting of high progesterone results in a sudden decrease and worse outcomes compared with mild TBI in the setting of low progesterone. Women, therefore, may experience worse outcomes than men because men have consistently low concentrations of progesterone. Although this theory still needs to be tested, researchers conducting TBI clinical trials could consider determining menstrual phase at time of injury and controlling for this variable when determining the effect of treatment on outcomes.

While studies of cellular and molecular factors have begun to address sex-based differences, at the systems level, most research still focuses exclusively on males. This includes research on outcomes from rehabilitation. For treatments that involve rehabilitation, it is important to understand sex- and gender-based differences in behavioral functions that may influence the rehabilitation process. Return-to-work experiences after TBI, for instance, have been found to vary by gender.[128]

One area in particular in which sex- and gender-based differences may be critical is in social functioning,[129] that is, the ability to successfully engage in social interactions, and achieve desired social participation and quality of life, limit rehabilitation benefits, and compound injury effects on outcome after discharge. There is a common “folk wisdom” that females (defined by sex or gender) have better social skills than males. If true, this difference could affect rehabilitation outcomes in important ways. Females could have more capacity (ie, social “reserve”) and thus have better social outcomes than males from equally severe injuries. Evidence of a female advantage includes superior performance on basic social cognition tasks and communication tasks in females versus males, with or without TBI.[130,131] Alternatively, women could be more symptomatic, or at least more aware of their social deficits. This notion is supported by evidence that females with TBI report more everyday social communication problems than males, and women’s self-evaluations are more congruent with those of their caregivers than are men’s.[132] Effects of social impairments in women could be compounded by societal expectations: if people expect women to have better social skills, then even relatively mild impairments might have great social penalties for women.

When people with TBI are asked what is most important to them in life, social participation tops the list. More than 6 decades of TBI rehabilitation research has established methods to support social participation in males. Whether these same methods work for females is yet to be determined.

Suggestion: Prioritizing rigorous assessment of physiological and functional markers of injury and recovery in female and male subjects would enhance our understanding of the basic biology of TBI. Studying sex and gender differences in outcomes after TBI may help identify protective and detrimental factors related to recovery. The following would be promising areas of inquiry:

1. Thoroughly characterize the fluid biomarker dynamics related to phase of menstrual cycle and life stage.
2. Incorporate assessment of hormonal status into all TBI studies.

3. Define/develop/characterize sex-appropriate outcome measures for both clinical and preclinical studies to reduce inherent bias in assessments following TBI.
4. Adequately assess preclinical and clinical trials for sex- and gender-related differences in outcomes and rehabilitation efficacy.

CONCLUSION

Over the years, despite the growing number of studies examining a range of factors related to TBI, there remains relatively little research on females or sex and gender differences. The information provided in this report makes it clear that a better understanding of all 3 of these is critical for optimal assessment, intervention, and rehabilitation of females who experience TBI.

Clinical research has identified various sex-specific biological and psychosocial outcomes for individuals recovering from TBI as well as potential protective factors for women. However, while many studies have focused on sex-related differences following sports-related concussion and military blast injury, there remains a paucity of literature on violence-related TBI in women. IPV is a gender-based issue, and data indicate that a substantial number of women who have experienced physical IPV have sustained a BI from an abusive partner. Population-based studies examining the true prevalence and effects of such brain injuries are critically needed.

The biologic underpinnings of sex differences are both complex and understudied. In the preclinical literature, sex-based or sex hormone–associated differences have been documented in brain structure, cerebral blood flow, autonomic response, mitochondrial dynamics, and neuroinflammatory response, all of which may contribute to sex-based differences in outcomes after TBI. Preclinical studies may offer unique opportunities to study mechanisms of sex-based differences, but, to date, the vast majority of preclinical TBI studies have investigated exclusively male subjects. Recent NIH mandates to account for sex as a biologic variable will hopefully drive mechanistic studies related to sex differences.

There is a need for education on the integration of sex and gender in research. While study populations are increasingly diversifying, study participants are still predominately cisgender, with very few evaluating psychological or psychosocial outcomes after TBI for transgender or nonbinary populations.[133] As these individuals disproportionately face violence, it follows that they may be experiencing the effects of BI as well. Ultimately, an understanding of sex- and gender-based differences following TBI may contribute to further developments in precision medicine and individualized care.

Furthermore, there also exists heterogeneity in research results and thus sex and gender influences are difficult to disentangle. A recent review by Mollayeva and colleagues[7] provides a framework by which to assess heterogeneity in these studies. The review focuses on sex, gender, and TBI in vulnerable populations. Reviewed findings suggested that gender-sex interactions predict rates and severity of TBI, as well as help-seeking and healthcare usage, again underscoring the importance of understanding the intersectional nature of sex, gender, and TBI. As such, sex and gender should be considered in manuscript review

and publication. Both the NIH and the Canadian Institutes for Health Research websites have considerable resources on the topic of sex and gender that are freely available. The SAGER guidelines that address sex and gender considerations in assessing manuscripts when submitted to journals are also an important resource.[134] For example, authors should justify inclusion or exclusion of males or females in their study, and the resulting data should be stratified by sex and/or gender when appropriate. As previous work has found that among 200 studies on mild TBI, only 7% included sex-stratified data,[135] this issue is particularly relevant to the BI literature. Policies and guidelines such as SAGER may help reinforce the importance of diverse research populations and guide researchers to evaluate the implications of results.

Furthermore, because there is evidence of sex differences in recovery from TBI, it would be helpful to tailor educational materials by sex. As for patient education, it is important that knowledge transfer materials (eg, websites, brochures) consider sex and gender. For example, a brochure on female reproductive health outcomes for women with a TBI and their families, based on work from Colantonio et al,[136] indicated that menstrual cycle disruption was common among women after moderate to severe injury up to 10 years postinjury. Recently a web-based toolkit has been developed, addressing significant knowledge and practice gaps[137] relevant to TBI specifically relevant for frontline providers supporting abused women (www.abitoolkit.ca). Recent research has highlighted perceptions of sex, gender, and TBI relevant to clinical practice by both patients and clinicians that should inform knowledge transfer materials and future research.[138-141] TBI service users have expressed differential preferences for care by sex.[142] Such data and materials may help disseminate sex- and gender-specific research findings in clinical and other settings. Current studies are underway to addressing the impact of implementing sex- and gender-informed knowledge transfer materials as this is currently a gap in the literature.[143]

Notably, while this summary of the current literature is extensive, it is not meant to be a scoping review of all sex differences in TBI research. Here, we sought to summarize and update information on the topics discussed at the NIH “Understanding TBI in Women” workshop.[144] We focused not only on *sex differences* but also on studies including *only females*, for which this review clearly shows there is a paucity of research. We refer to another recent review[5] on sex differences primarily in adults of reproductive age for a systematic review of *sex differences*.

We conclude with some “common suggestions” relevant to all groups and populations discussed in this article.

1. Enhanced implementation of the NIH Policy on Sex as a Biological Variable when designing, reviewing, and conducting TBI studies in humans and animals would increase inclusion of females in both clinical and preclinical research.
2. Inclusion of assays and assessments for determining hormonal levels at each period of data collection.
3. Assessment, analysis, and reporting of reproductive stage (prepubertal, postpubertal, and postmenopausal).

4. Analytic plans that include analysis to provide inference for sex as a variable rather than factoring out sex-based variability or simple dichotomization of sex as a factor. This would also include prespecifying and powering for sex difference analyses in the analytic plan.
5. Inclusion of sex-specific social environment factors in the use and development of assessments and outcomes in both clinical and preclinical TBI research and potential interactions with these measures.
6. Defining TBI and head impact exposures and determining whether exposure measures should be modified on the basis of sex.
7. Development of blood-based and neuroimaging diagnostic, prognostic, and predictive biomarkers tailored to sex-related biosocial factors and comorbidities.
8. Encouraging cross talk and interdisciplinary collaboration between TBI and experts in sex differences research.
9. Developing a knowledge base for sex differences in TBI incidence, prevalence, and outcomes.
10. Developing a life course perspective to assess the timing of TBI exposures and how they may interact with sex-specific developmental stages.

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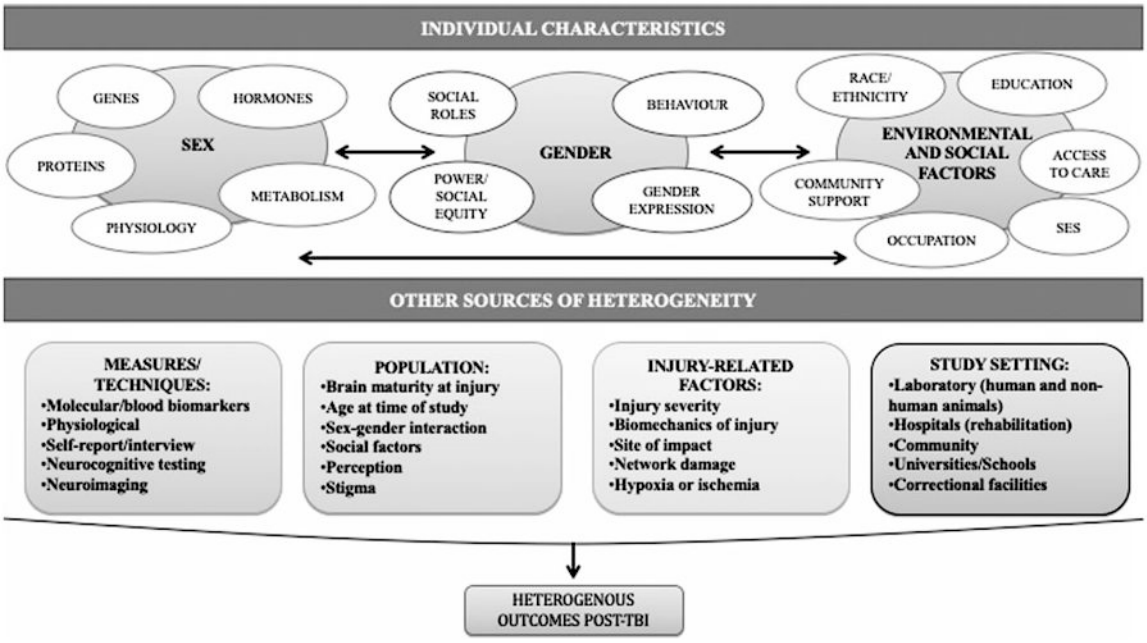

Figure 1.

Flowchart summarizing the interrelated constructs of sex and gender, specifically in the context of traumatic brain injury. Relationships are depicted bidirectionally (↔). Adapted with permission from Mollayeva et al.[7] SES indicates socioeconomic status; TBI, traumatic brain injury.