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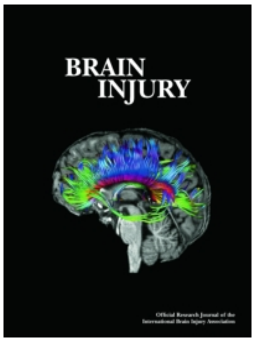

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Sex differences in concussion: a review of brain anatomy, function, and biomechanical response to impact

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ABSTRACT

Objective: Provide a potential explanation for sex differences associated with concussions.
Research Design: Review of current literature from complementary disciplines to synthesize a theory to explains sex differences in individuals with concussion.
Methods: Systematic review focusing on sex-related differences in individuals with concussion. Articles published in peer-reviewed journals after 2000 were reviewed and discussed among the authors to determine common themes across the different disciplines represented in the literature review.
Results: There are differences in brain structure between sexes. The male corpus callosum has larger fibers and cross-sectional area compared to females. Females tend to utilize both hemispheres of the brain for most tasks, while males are more lateralized. Computation models of concussive impacts indicate that the greater strains occur at the corpus callosum. The corpus callosum is the conduit for interhemispheric connections within the brain; therefore, it stands to reason that increased strain in this area may affect interhemispheric communications resulting in a difference in perceived symptoms between males and females.
Conclusions: Strain injury of the corpus callosum may affect females to a greater extent since their ability to process information may become more disrupted than males.

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Introduction

Over the past three decades, the interest in concussions especially in the field of sports medicine has increased dramatically (1). No longer are these injuries considered to be trivial and inconsequential (2). No longer do people believe that concussions are just part of the game; something that can be "shaken off" or downplayed as a "bell ringer" (3). Instead, concussions have seen a paradigm shift in which concern over concussions has pervaded main stream media, movies, and day-to-day conversations (4). The tenuous relationship in the media between concussions and chronic traumatic encephalopathy (CTE), as well as a concussion's ability to interfere with day-to-day activities has become a major concern for adults and children alike. This increased awareness has driven an enormous amount of research to try and elucidate the causes of a concussion, understand the clinical course of recovery, and if possible to try and prevent concussions from occurring.

Currently, medical research has focused on understanding the short and long implications of a concussion (5–7), as well as education and prevention efforts. This has resulted in a large body of literature describing the presentation and clinical course of sport-related concussions (8). However, other disciplines, such as mechanical and biomedical engineering, have attempted to understand the potential for unseen brain damage using sophisticated computer modeling to identify areas of increased stresses and strains across axonal pathways. Furthermore, research in the area of neurobiology has studied brain anatomy and has begun to incorporate diffusion tensor imaging, 3T MR imaging, and functional MRI to understand how concussions may affect both the brain's anatomy and function.

Yet, with this growing body knowledge, there are a number of remaining clinically important questions. One of the most important questions revolves around the observation that concussions effect males and females differently (9,10). Females tend to report a greater number of symptoms for a longer period of time than their male counterparts (11). Additionally, females seem to have different symptom clusters than males. Although some have postulated that females are more willing to disclose symptoms (12), other studies have proven there are no differences in the number of symptoms reported between sexes (10,13). Many researchers have postulated that the difference in female and male concussions is due to differences in brain anatomy and function, hormonal influence, or cervical muscle weakness. This has resulted in hundreds of papers across wide ranging disciples that are all trying to find the answer to the same question. Therefore, the purpose of this paper was to provide a comprehensive review of recent literature that discussed differences in male and female brain anatomy and function that might provide a potential explanation for the sex differences associated with concussions.

Methods

A systematic literature review was performed in January 2018 using PubMed, Google Scholar, and Compendix. The search

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terms were specifically chosen for the primary areas of interest which encompassed finite element analysis of the brain following an impact, gender/sex differences in concussion, and differences in brain anatomy and function between sexes. The search terms included various combinations of the following: concussion, symptom severity, gender/sex differences, brain anatomy, finite element analysis, adolescent concussion, fMRI, corpus callosum, diffusion tensor imaging, axonal strain, and hemispheric communication, mTBI, sports-related concussion. Articles were included if they were published in a peer-reviewed journal, written in English, and published after 2000. Additionally, review papers, case studies, case series, papers in which the population was not described, the average population age was over 30 years old (with a noted exception for the fMRI and diffusion tensor literature), the cause of the concussion was not sport related, or the sport requires one athlete to concuss the other (i.e., boxing, mixed martial arts) were excluded from the review. Papers were also excluded if they were consensus statements, editorials/letters to the editor, animal-based studies, or discussed biomarkers (Figure 1). It is important to note that populations over the age of 30 were excluded to provide a more homogenous group of young adults that were actively participating in sports. The decision to exclude papers concerning biomarkers was made by the senior author to keep this paper focused primarily on anatomic and functional differences in male and female brains.

Full-length articles were reviewed by the authors. In an effort to reduce bias, the authors each reviewed a different set of articles that most closely represented their area of expertise. For instance, MS reviewed the engineering-based papers, while HR reviewed the neuroanatomy papers. Each author then provided the senior author with a bullet point review of the articles and together the research team looked for common themes across all articles that could provide a plausible explanation for the differences seen between male and female concussion.

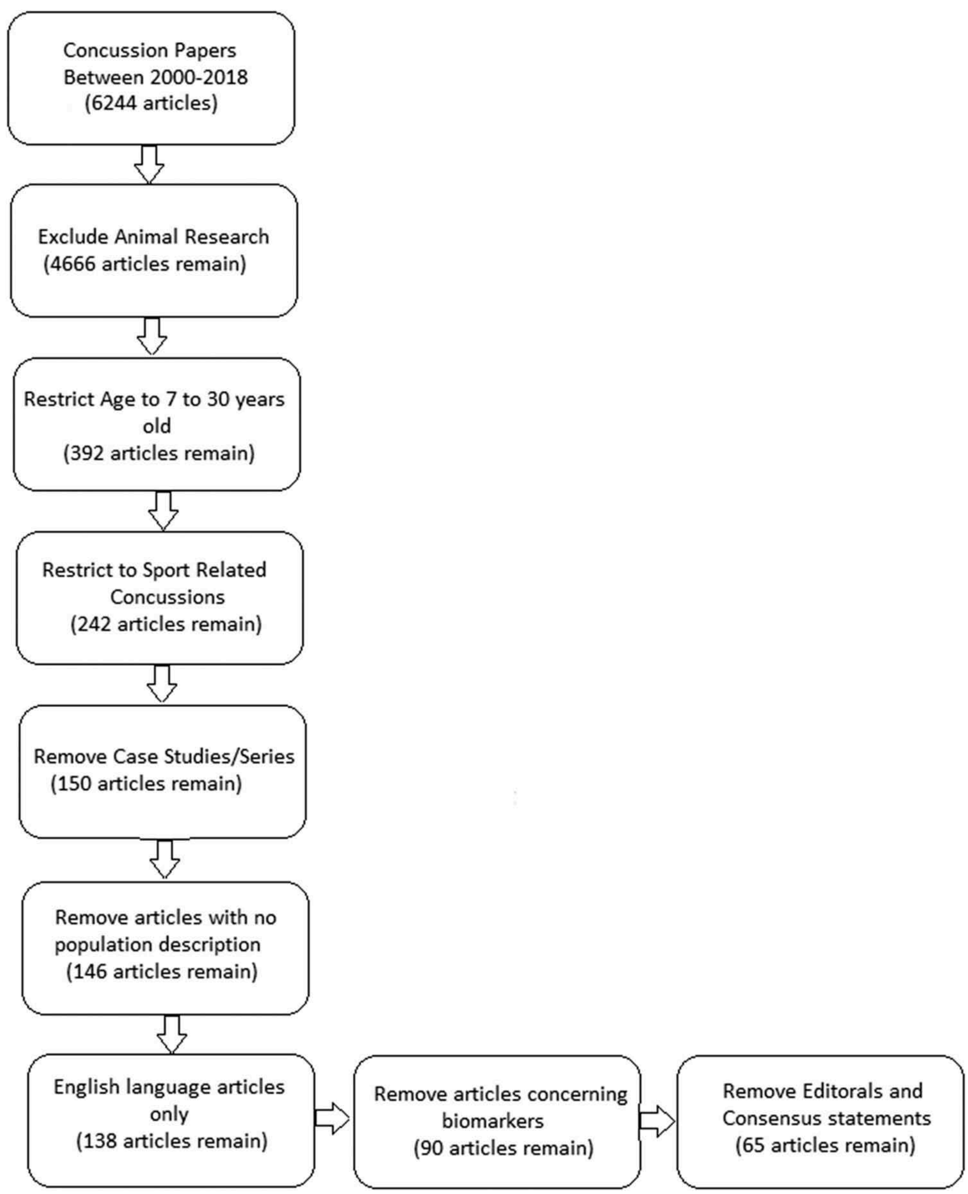

Figure 1. Depiction of selection process for the papers reviewed in this paper.

Results

The initial search resulted in a total of 162 papers that met inclusion criteria. After a review of the abstracts, this number was reduced to 65.

Sex differences in concussion

Concussions account for 5.9–9% of all sport-related injuries in high school and collegiate level athletes (7,14). Although male-dominated sports such as football still produce the highest rates of concussion; sports in which males and females compete equally, such as soccer, lacrosse, and basketball, have shown that females experience more concussions during games than their male counterparts (9.5% versus 6.4%) (6). Interestingly, few studies have noted differences in the severity of the concussion, but they have noted that females tend to report a greater number of symptoms and have a different constellation of symptoms than males suffering from concussions (14,15). Broshek et al. reported that females experienced greater declines in cognitive function and indicated a greater number of symptoms both subjectively and objectively measured than males (14). Additionally, Broshek et al. noted that females reported 1.7 times more cognitive issues including difficultly concentrating compared to males (14). Covassin et al. reported that females present with more concussion symptoms and take longer to recover than males (15). Additionally, they reported that females were noted to have slower reaction times and twice as likely to report cognitive symptoms (15). A number of other studies have also shown similar results specifically in reaction time, cognitive function, and verbal tasks (16–18).

Sex differences in neural function and anatomy

It has long been noted that there is an obvious size difference between male and female brains; however, when adjusted for body size the male brain is still slightly larger than the female brain (19). Several other differences have also been noted, but most relevant to this paper are the differences concerning the corpus callosum and concentration of gray matter. There are a number of discrepancies concerning differences of brain structure sizes most notably the idea that women have a smaller corpus callosum than men (20). However, this concept has proven to be rather controversial given that a number of studies have indicated that the corpus callosum is the same size when comparing the two sexes especially when accounting for the overall difference in brain size (21). Yet, most studies do agree that there are differences in brain anatomy between men and women. Men have more gray matter than white matter which indicates more active neurons, while women have more white matter suggesting a greater communication between different areas of the brain (22–24). Additionally, a number of studies agree that the corpus callosum is shaped differently, males have a more cylindrically shaped corpus callosum, while female have a more bulbous shape (25,26). Finally, the corpus callosum's cross-sectional area is larger in men than in women (25,27) which is primarily caused by a greater number of large diameter (3 μm) myelinated axons compared to the smaller non-myelinated axons (1–3 μm) in females (21,28,29). However, it is important to point out that although males have thicker fibers, females have a greater number of fibers crossing the corpus callosum suggesting greater interhemispheric communication (21,24,25,28).

Studies have suggested that males tend to be single hemisphere dependent for most tasks, while females tend to be bi-hemisphere dependent (30). A study by Nowicka et al. indicated that interhemispheric transmission times for verbal information were similar for both left to right and right to left in females but considerably longer (three times) from left to right in males (30). Similarly, Zaidi et al. indicated that women use several parts of their brain when engaging in single tasks suggesting a greater amount of integration and more complex connections than males (24). Zaidi presents the example that males and females process singular words in a similar fashion but when processing an entire sentence women use both hemispheres, while males use one (24). Recent fMRI studies have suggested that males have stronger lateralized activations compared to females when performing verbal and verbal memory tasks (31–33). Women tend to have stronger networks consisting of bilateral superior prefrontal and mid-inferior temporal activations suggesting that females recruit multiple areas of both hemispheres, while males active one hemisphere with limited interhemispheric communications (31–34).

Finite element analysis

In the past two decades, there have been a number of advances in computer simulation that has allowed researchers to build complex finite element models of the brain to describe the brains response to externally applied forces. Although there are a number of different models in the literature, such as the Wayne State University Brain Model, the KTH Finite Element Human Head Model, the results from these studies are remarkably similar. The similarities in the results despite different modeling parameters and minor differences in material properties and assumptions lend greater credence to the conclusions drawn from this body of literature. The majority of the studies looked at impact data recorded from sports collisions using either the accelerometer-based systems (35–40) or video reconstruction methods (39,41–43) that resulted in concussions. The impact data were then entered into the models and the areas of maximal strain, strain rates, and shear were evaluated. All of the studies indicated that the greatest concentrations of shear and strain were located in the corpus callosum (35–39,41–44), midbrain (35,38,40), and thalamus (35,38). Therefore, the authors of these studies concluded that the corpus callosum is the primary area for axonal injury following a concussive impact, with increased strain and strain rates of the corpus callosum correlating with removal from play (36,39). Ng et al. theorized that the increased strain on the corpus callosum was likely the cause for the neurobehavorial sequelae of an mTBI, specifically the reduction in attention, reaction time, and working memory (37). Additionally, Viano et al. noted that memory and cognition problems occurred most often when the strain rate in the corpus callosum (fornix) was greater than 3050% of the total applied forces (39).

Discussion

Concussions are complex injuries that do not fit into a simple clinical algorithm when it comes to both presentation and management. Rather presenting symptoms and the subsequent clinical course are unique with each and every patient. Literature has shown that not only is there a large variation between children, adolescents, and adults suffering a concussion but there are also large differences between sexes as well. This complexity should give medical professionals pause as they try to elucidate the best means of treating concussions for their individual patients.

The collective interest in concussions across a variety of disciplines has created an extensive body of literature that provides a wealth of knowledge regarding concussion. However, it is common to look only at the literature that is similar to your own research interests and as a result some of the broader connections between different disciplines are lost. Therefore, in this paper we have attempted to better describe the anatomical and functional differences of the brain between the sexes, as well as looking at information from computer simulations that describe the areas of the brain most affected by concussion, and postulate another plausible reason for the sex differences noted in concussions. By understanding these differences between males and females, we can better explain the differences seen following a concussion.

This paper has shown that the major difference in male and female brains is that the female neural network makes greater use of both hemispheres traversing larger areas of the brain to perform a variety of tasks, whereas males tend to be more lateralized using a single hemisphere to accomplish many of these same tasks. Additionally, the brain structures between males and females are also different, especially with regard to the corpus callosum, neuronal morphology, percentage of gray matter, and overall brain size. While there is no true size difference in the corpus callosum between the sexes, the cross-sectional area, axons, and axon fiber type are different. Males tend to have fewer but thicker myelinated fibers crossing the corpus callosum, while females tend to have small diameter fibers but a greater number than found in males. The thicker fibers found in males could be the contributing factor as to why they have a greater cross-sectional area to their corpus callosum and may contribute to increased integrity. The increased number of fibers in the corpus callosum that has been noted in females could be due to the more extensive neural networking required to enhance communication between the hemispheres of the brain.

The results of the finite element analysis have shown that impacts resulting in concussions often produced the greater shear and strain in the corpus callosum. This increased stress on the corpus callosum can lead to axonal damage and consequently a greater number of and more concussion symptoms such as reduced concentration, dizziness, and decreased verbal and working memory. Interestingly, the area that shows the greater chance for axonal damage is also the one structure in the brain that is most different between males and females. Given the larger cross-sectional area, larger fiber diameter, and greater number of microtubules in the axon in males, it may be possible for males to withstand larger axonal stresses than females, thus contributing to less axonal damage. Additionally, the corpus callosum is the primary gateway connecting the left and right hemispheres. Because females rely on greater interhemispheric connections, any disruption to this neural network from axonal strain may cause different symptoms between males and females. If axonal function is reduced or slowed the communication between the hemispheres, then it stands to reason that females would be affected to a greater extent than males as males do not rely on as much cross hemisphere connectivity. This could also point toward why females appear to take longer to recover than males from concussions.

This review paper is not without limitations. Only a small sample of the copious amounts of literature on this topic were reviewed. Additionally, it was the intention of the authors to specifically limit the age range for this review to papers with average population ages of 30 years old or less. This provided a more homogenous group that was experiencing sport-related concussion. However, this does limit the generalizability of the review to only this population, as there may be some differences in older populations or individuals with non-sport -related concussions.

In conclusion, we postulate that the robust interhemispheric processing present in the female brain is, by default, more corpus callosum dependent, and the corpus callosum is a site of increased strain and axonal injury flowing a concussion. It is not unreasonable to believe that because the female and male brains are wired differently that concussions would then affect the sexes differently. Following the common corpus callosum strain injury seen in concussions females would perceive the injury differently than males since their ability to process information, as well as their neural networks become more disrupted than males. As there is a functional difference between the male and female brains and as our understanding of concussions evolves, it seems reasonable to believe that the diagnosis as well as future treatments may be tailored differently for the sexes.

Disclosure statement

No potential conflict of interest was reported by the authors.

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