EXPLORING THE POTENTIAL ROLE OF SEX-BASED BRAIN STRUCTURAL VARIATIONS IN SUSCEPTIBILITY TO TRAUMATIC BRAIN INJURY FROM A BIOMECHANICS PERSPECTIVE

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INTRODUCTION

Sex differences in the human brain neuro-structure are increasingly recognized as one of the underlying factors contributing to the sex variations in the prevalent incidence, onset, and development of neurological disorders and brain injuries [1]. In particular, when it comes to traumatic brain injury (TBI), studies using finite element models (FEM) of brain have shown that the overall and regional differences in brain structure can directly or indirectly affect how the brain deforms under head biomechanical loadings during traumatic events [3, 4]. Furthermore, the brain deformation is proven to be correlated with the occurrence and pathology of TBI [2]. For instance, a brain FEM study showed that applying the same impact kinematics to head models with different sizes, or the same size but a different shape, resulted in different peaks and distributions of strain especially in the corpus callosum (CC), a critical location for traumatic axonal injury [3]. Another FEM study investigated the mitigating role of cerebrospinal fluid (CSF) under head injuries and showed that CSF reduces maximum brain strains and provides a protective buffer against impacts [4].

Although there are evident sex-related differences in various brain regions, research exploring these differences at both the macro- and meso-scale levels remains limited and all the previously developed FEMs of brain have been biased toward males. Moreover, we have previously shown that these sex-based structural differences cannot be addressed by global and uniform scaling [1]. Therefore, in this study, we aim to investigate the anatomical features and volumetric measurements of brain (macroscale), along with diffusion tensor imaging (DTI) metrics and the connections between brain regions (mesoscale), to explore sex-specific variations in the brain structure from biomechanics perspective. Such information is crucial for future studies involving FEMs in the field of brain biomechanics particularly when examining the impact of sex-specific differences on the onset and outcomes of TBI.

METHODS

In this study, subcortical brain segmentation was performed on magnetic resonance images (MRI) from 500 females and 500 males using the FreeSurfer software. The details about dataset used herein can be found in [1]. The final brain masks had the size of 256×256×256 with a voxel size of 1.0 mm×1.0 mm×1.0 mm. The total brain volume (TBV) along with the volume of several regions including CC and CSF were calculated for all subjects. The absolute volumes of the segmented regions were normalized by the TBV of each subject to obtain the fractional volumes and investigate whether the sex variations are proportional to the TBV. The sex-based structural differences were evaluated by the Mann-Whitney test with a significance level of $p=0.05$.

The diffusion-weighted MRIs of the same dataset underwent DTI analysis and fiber tractography using DSI-Studio software. The orientation distribution functions for images were aligned using subject-specific frameworks, employing Q-space diffeomorphic reconstruction technique. These frameworks were generated by a nonlinear registration of widely-used ICBM-152 T1-common space to T1-MRI head from each subject image. “FreeSurferSeg” atlas in DSI-Studio was adapted to optimize the best selection of regions in brain tractography resulting in the 23 regions of interest (ROIs). These regions include Corpus callosum (CC), Left Cortex (L-Co), Left Cerebral white matter (L-Cr-WM), Left Cerebellum white matter (L-Cb-WM), Left Cerebellum grey matter (L-Cb-GM), Left Thalamus (L-Th), Left Putamen (L-Pu), Left Pallidum (L-P), Left Hippocampus (L-Hi), Left Amygdala (L-Amg), Left Accumbens (L-Ac), Brainstem (BS), Optic chiasm (OX), Right Cortex (R-Co), Right Cerebral white matter (R-Cr-WM), Right Cerebellum white matter (R-Cb-WM), Right Cerebellum grey matter (R-Cb-GM), Right Thalamus (R-Th), Right Putamen (R-Pu), Right Pallidum (R-P), Right Hippocampus (R-Hi), Right Amygdala (R-Amg), Right Accumbens (R-Ac), Cerebrospinal fluid (CSF). We also mapped the refined atlas to the common space of each individual subject. Fiber tracking was then conducted on each subject in DSI-Studio, employing

Euler tracking algorithm [5]. For each subject, scaler metrics including fiber anisotropy (FA) and mean diffusivity (MD) were derived and the brain connectivity matrix was calculated using 1000000 fiber tracts. The matrix cells (count*FA) were calculated using the count of connecting tracts passing through pairs of regions multiplied by the mean FA values measured on those tracts as a quantification of connection strength between the two ROIs. Independent-samples Mann-Whitney U tests were performed on DTI metrics and the pair-wise connections to examine the distribution of these metrics for all 23 brain regions across the two categories of sex.

RESULTS

Significant difference was observed in the distribution of TBV between male and females with males having larger values and wider distribution compared to females (Figure 1). In addition, the distribution of both the absolute and the fractional volume of CC was significantly different across sexes, and female population was observed to have a larger CC, proportional to their brain. Regarding CSF, while the fractional volume distributions were mostly similar across sexes, the absolute values were noticeably higher in males.

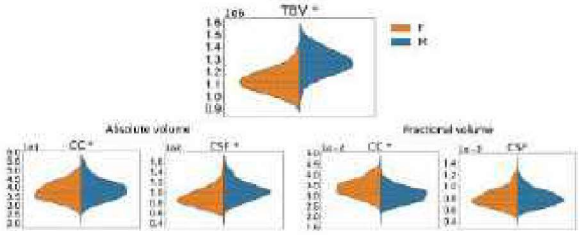

Figure 1: Sex-based comparison of the distribution of volumes for TBV, CC, and CSF. The asterisk * symbol shows a statistically significant difference

The difference values between mean regional FA and MD in females and males (Figure 2) shows that FA values are significantly larger in majority of regions with highest difference in CC which is known as the largest white matter structure. This trend was the opposite for MD values. These significant differences were observed in 70% and 91% of the regions for the FA and MD values, respectively.

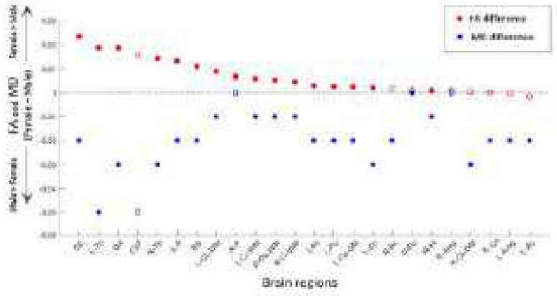

Figure 2: Sex differences in the FA and MD values (median of population) across brain regions. Filled markers denote regions with statistically significant differences ($p < 0.05$)

The heatmap shown in Figure3-a indicates that in 70% of the region pairs, there is a significant sex difference in the brain connectivity (count*FA). The strength connectivity difference matrix between female and male populations (Figure3-b), obtained by subtracting their respective median connectivity matrices (count* FA), shows stronger connections, including interhemispheric white matter and those from left and right cortical regions, passing through CC, in females compared to males.

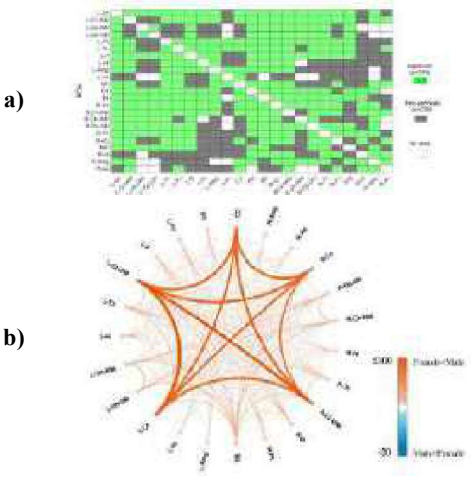

Figure 3: a) Statistical comparison of the component of brain connectivity matrix between female and male subjects (green shows significant difference), and b) the median female-male connectivity difference matrix (count* FA)

DISCUSSION

The distribution of volumetric parameters as well as the DTI metrics and the strength of connections were significantly different for most of the brain regions across males and females. Due to such intricate sex-based structural variations at macro- and meso-scales, and the inaccuracy of global linear scaling [1], developing separate brain templates and FEMs for males and females are highly encouraged to investigate sex-specific TBI mechanisms and protection interventions.

Exploring sex-specific brain vulnerability to TBI reveals different patterns at both macroscale and mesoscale levels. From the macroscale perspective, males have a larger brain volume potentially leading to greater deformations during impacts, making them more susceptible to TBI. This is further supported by the smaller fractional volume of CC, indicating higher vulnerability in males. However, the larger absolute volume of CSF in males may provide better cushioning, mitigating the risk of TBI in males. On the mesoscale, females exhibited higher FA values for most ROIs and stronger inter-hemispheric connections which could influence their TBI exposure differently. Furthermore, larger volume and higher FA for CC as well as its stronger connections in females may suggest a lower susceptibility to TBI in CC in females.

All in all, our findings may suggest a possible higher TBI vulnerability in males compared to females undergoing same head kinematic accelerations from brain structure perspective. However, this possibility may be counterbalanced by the sex-based variations in head kinematic severity and hormonal dynamics. The interaction of sex-specific brain FEMs with further biological research is promising to unravel such complex interplay of factors influencing TBI vulnerability in males and females.

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