Functional connectivity of the anterior cingulate cortex in Veterans with mild traumatic brain injury

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\begin{abstract}
\textbf{Background:} Traumatic brain injury (TBI) is one of the most prevalent injuries in the military with mild traumatic brain injury (mTBI) accounting for approximately 70–80\% of all TBI. TBI has been associated with diffuse and focal brain changes to structures and networks underlying cognitive-emotional processing. Although the anterior cingulate cortex (ACC) plays a critical role in emotion regulation and executive function and is susceptible to mTBI, studies focusing on ACC resting state functional connectivity (rs-fc) in Veterans are limited.

\textbf{Methods:} Veterans with mTBI (n = 49) and with no history of TBI (n = 25), ages 20–54 completed clinical assessments and an 8-minute resting state functional magnetic resonance imaging (rs-fMRI) on a 3 T Siemens scanner. Imaging results were analyzed with left and right ACC as seed regions using SPM8. Regression analyses were performed with time since injury.

\textbf{Results:} Seed-based analysis showed increased connectivity of the left and right ACC with brain regions including middle and posterior cingulate regions, precuneus, and occipital regions in the mTBI compared to the non-TBI group.

\textbf{Conclusions:} The rs-fMRI results indicate hyperconnectivity in Veterans with mTBI. These results are consistent with previous studies of recently concussed athletes showing ACC hyperconnectivity. Enhanced top-down control of attention networks necessary to compensate for the microstructural damage following mTBI may explain ACC hyperconnectivity post-mTBI.
\end{abstract}

1. Introduction

Mild traumatic brain injury (mTBI) is common among Veterans of Operations Enduring Freedom and Iraqi Freedom (OEF/OIF); approximately 15–25\% of Veterans and Service Members deployed to OEF/OIF report an mTBI event during deployment \cite{1,2}. Symptoms associated with mTBI includes vision and hearing deficits, posttraumatic stress and other mental health conditions, problems in cognitive and behavioral domains, orthopedic injuries, internal organ dysfunction, and a range of other long-term health problems, which are collectively referred to as post-concussive symptoms \cite{3}. Further, mTBI is associated with increased mortality, neurodegenerative disorders, stroke, epilepsy, hypertension, coronary artery disease, and diabetes \cite{4}. Further, it has also been shown to increase risk of suicide, posttraumatic stress disorder (PTSD) and other mental health conditions as well as deficits in several cognitive domains \cite{4–7}. Symptoms following mTBI have been reported to resolve quickly in some cases; however, there have been an increasing number of studies demonstrating that symptoms and cognitive deficits may persist for several years in some individuals \cite{8–10}. Amongst the subclasses of TBI, mTBI is often the most difficult to diagnose, partly due to the lack of clinically measurable outward signs of injury, making it difficult to understand disease progression. Most investigations of mTBI have focused on the acute period immediately following the injury with fewer studies examining the chronic period, many years following the acute injury. The long-term effects of mTBI are a critical issue given the need for the healthcare system to care for an aging veteran population.

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Diffuse axonal injury (DAI) is a frequently observed in mTBI and has been shown to affect large white matter trajectories resulting in disruption of interaction between spatially distinct brain regions [11, 12]. This structural change suggests mTBI may alter the functional connectivity (fc) between resting state networks, which can be investigated using resting state functional MRI (rs-fMRI) technique. Several studies have demonstrated altered resting state functional connectivity (rs-fc) in several brain networks in civilian mTBI. One network that has consistently been implicated in TBI is the default mode network (DMN). The DMN exhibits relative hypoactivity during cognitive and stimulus-driven tasks, and is most active at rest [13]. Some of the main functions of the DMN involve self-referential thought and other introspective processes—activities that predominantly occur at rest [13]. Structurally, this network consists of core regions in the posterior cingulate cortex (PCC), the rostral anterior cingulate cortex (rACC), ventromedial prefrontal cortex (vmPFC), and medial temporal lobe [14]. The DMN is vulnerable to traumatic injury because it is highly dependent on functional connections between brain areas that pass through midline areas that are susceptible to shear/strain injury [15]. Reduced connectivity within the DMN and increased connectivity of the DMN with other regions such as the lateral prefrontal cortex in the sub-acute period (4–5 months after injury) has been observed in civilian mTBI [16]. In addition, increased fc in the DMN [17] as well as reduced fc in other networks [18] has previously been demonstrated in individuals with civilian mTBI. Furthermore, in civilians with moderate and severe TBI, stronger rs-fc in five resting-state networks (sensory-motor, visual, posterior part of the DMN, executive control network, and cerebellum) has been observed [19]. Thus TBI has widespread effects involving both higher order cognitive networks as well as sensory networks.

Rs-fMRI of mTBI studies in Veterans and active duty personnel have produced inconsistent results. In a study of 13 Veterans with blast-related mTBI, Vakhtin and colleagues reported disrupted fc of the DMN as well as frontal and attentional networks using an independent component analysis (ICA) approach [20]. Another study showed that it was the proximity to the blast that was associated with the disrupted connectivity of the DMN rather than the presence of the concussive symptoms [21]. Using an ICA approach, Nathan et al. reported increased connectivity within posterior regions of the DMN in Active Duty Service Members without a PTSD diagnosis who had a maximum of one mTBI and were between 2 and 10 months post-injury, relative to Active Duty Service Members with no history of TBI [22]. This study also demonstrated an increase in connectivity in the supplementary motor area and the cerebellum. Divergent results can be attributed to several reasons including time of observation since injury, the type of injury that caused the TBI, and the type of TBI. Furthermore, in a Veteran population, the presence of comorbidities such as PTSD, mood disorders, and substance use disorders as well as concomitant medications are additional confounding factors. Furthermore, study methods applied to studies of mTBI have used a range of methods introducing additional sources of heterogeneity [23].

The anterior cingulate cortex (ACC) is a region that is particularly susceptible to TBI through diffuse axonal injury and Wallerian degeneration [11, 24]. The ACC has been implicated in several cognitive processes including emotion, attention, reinforcement learning, reward and error processing [25]. The ACC demonstrates a great deal of heterogeneity in its cytoarchitecture and functional connectivity. Specifically, the central portions are more involved in emotion processing whereas the dorsal portions are involved in cognitive processing [26]. Although a clear segregation of emotional and cognitive functions may be less likely, the rostral ACC (rACC) is implicated in conflict monitoring, the pregenual ACC (pgACC) is implicated in social processing and the most ventral subgenual ACC (sgACC) is implicated in emotional processing [27]. Not all studies investigating dysfunction of the ACC in TBI have focused on a particular subregion of the ACC. One imaging study reported bilateral atrophy of the ACC in individuals with mTBI a year post-injury [28]. Task-based functional studies have revealed increased activation in the ACC during stimulus-response incompatibility in blast-related mTBI [29]. Furthermore, error processing in blast-related mTBI was associated with enhanced negative coupling between the DMN and the dorsal ACC [30]. Rs-fc studies investigating the ACC have shown altered connectivity with several key regions of the brain including hyperconnectivity of the rACC and lateral prefrontal cortex in civilian mTBI [16]. Damage to the ACC as a result of TBI may explain several common TBI-related sequelae, which include altered emotional, memory, and executive control.

Given the pervasive role the ACC plays in emotion regulation and executive function and its implication in the pathophysiology of mTBI sequelae, our goal in the current study was to investigate the rs-fc connectivity of the ACC in Veterans with mTBI using a seed-based approach.

2. Methods

2.1. Participants

The Institutional Review Board at the University of Utah and George E. Wahlen Department of Veterans Affairs (VA) Medical Center approved this study. All participants provided written informed consent and were compensated financially for their time. Study participants were recruited from the George E. Wahlen Health Care System and the greater Salt Lake City area using advertising and word of mouth.

Participants in the study consisted of 49 Veterans with TBI (89.7 % male, mean age = 38) and 25 Veterans with no TBI (65.3 % male, mean age = 34.3). Participants were excluded if they had major sensorimotor handicap, estimated full scale IQ < 80, history of autism, claustrophobia, electroconvulsive therapy, active neurological disease, or any MRI contraindications. Participants were also excluded if they had a substance use disorder in the past 3 months. Due to ethical reasons, participants were not asked to stop taking medication. The proportion of participants on different classes of medication were as follows: anti-depressants including selective serotonin reuptake inhibitors, tricyclic anti-depressants (19 %), anti-anxiety including benzodiazepines and prazosin (12.5 %), sleep medications including anti-histamines (13.75 %), opioids for pain (25 %), non-steroidal anti-inflammatory drugs (51 %), other drugs for pain such as gabapentin (13.75 %).

2.2. Procedures

Participants were administered a battery of assessments including structured diagnostic interviews. The Ohio State University TBI Identification Method was administered to quantify presence, number, and severity of lifetime TBI. Severity of TBI was assessed according to parameters described by Belanger and colleagues [31]. Veterans were classified as having mTBI if they reported a head injury with an alteration of consciousness (AOC) up to 24 h or loss of consciousness (LOC) of 0–30 min. Moderate TBI was defined as an injury event with AOC between 24 h and 7 days or LOC between 30 min and 24 h. Severe TBI was defined as AOC greater than 7 days or LOC greater than 24 h. The TBI cohort primarily reported mTBI with only 4 subjects reporting additional moderate TBI. These 4 subjects were excluded from rs-fc analyses. mTBI was the primary focus of the study since majority of the participants reported mTBI and also because mTBI is the most common type of TBI in Veterans [1]. mTBI descriptive statistics included the number of total mTBI, the number of mTBI with LOC, the number of mTBI without LOC, the number of months since the most recent mTBI, and the number of months since the most severe mTBI experienced. Means, standard deviations, and ranges of these measures are displayed in Table 1.

Senior level clinical researchers have established good inter-rater reliability on the structured diagnostic interview and clinical research measures administered in the current study (kappa > 0.90). The
Structured Clinical Interview for DSM-IV-TR (SCID-IV-TR), a clinician-administered, semi-structured interview was completed to determine global assessment of functioning (GAF) as well as current and historical mental health diagnoses [32]. Given high rate of comorbidity between TBI and, anxiety, PTSD, and depression, participants also completed scales assessing these measures. The Hamilton Anxiety Rating Scale (HAM-A) [33] and the Hamilton Rating Scale for Depression (HAM-D) [34] are clinician scored quantitative measures that give a severity of anxiety and depression symptomatology respectively. The Clinician-Administered PTSD scale (CAPS) is a structured interview designed to make a categorical PTSD diagnosis, as well as to provide a measure of PTSD symptom severity. The Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II) was used as a brief measure to estimate the intelligence quotient (IQ) [35].

### 2.4. Functional MRI post-processing

FMRI images were analyzed using SPM8 (Wellcome Department of Imaging Neuroscience, University College, London, UK) and Data Processing Assistant for Resting-State fMRI (DPARSF) software running in Matlab (Mathworks, Natick, MA, USA). The first 10 volumes of functional images were discarded for signal equilibrium as well as to allow for participants adaptation to scanning noise. Initially, in order to correct for the head movement, all images were realigned to the first image using six degrees of freedom rigid body motion correction procedure [36]. The realigned images underwent spatial normalization into the Montreal Neurological Institute (MNI) template, followed by resampling to 3 mm cubic voxels and spatial smoothing using an isotropic 4 mm full-width at half-maximum Gaussian kernel. In addition, an estimate of head motion at each time point was calculated as the frame-wise displacement (FD), using six displacements from rigid body motion correction procedure, and motion “scrubbing” was applied to scans that surrounded a minimum of 0.5 mm displacement (one scan before displacement, two scans after displacement) using nearest neighbor interpolation [38, 39]. The average framewise displacement (FD) for the mTBI group was 0.237 ± 0.163 (mean ± standard deviation), while for the non-TBI group was 0.227 ± 0.139. There were no significant differences in mean FD between the groups (p = 0.4). Finally, linear regression was used to reduce the effect of nuisance signals (six head motion parameters, global signal, and signals derived from cerebrospinal fluid and white matter) [40, 41] and temporal band-pass filtering (0.01 – 0.08 Hz) was applied to reduce the effect of low-frequency drifts and high-frequency physiological noise.

### 3. Results

#### 3.1. Group differences in demographic and clinical measures

The demographic and clinical measures are depicted in Table 2. The sex distribution was significantly different between groups with more males in the mTBI group compared to the non-TBI group. Group differences in age and education showed a trend towards significance with higher age and education in the mTBI group. There were no significant between group differences in estimated IQ. With regard to the clinical characteristics, HAM-A, HAM-D measures as well as the CAPS and GAF scores were not significantly different between the mTBI and non-TBI groups (Fig. 1).

#### 3.2. Group differences in functional connectivity of ACC

The mTBI group exhibited greater rs-fc of the left and right ACC with the right posterior cingulate, the right precuneus, the left and right middle cingulate, the left supplementary motor area (SMA), and the left and right paracentral lobule than the non-TBI group (Table 3, bottom panel of Figs. 2 and 3). Furthermore, the right ACC in the mTBI group showed higher connectivity to the left and right superior occipital regions and the left precuneus, than the non-TBI group. These results demonstrated that the mTBI group showed increased connectivity of the
ACC with middle and posterior cingulate, occipital, somatosensory, and the precuneus, considered to be the hub of the DMN, as compared to Veterans with no TBI.

In addition, the two-sample \( t \)-tests between the mTBI and no TBI groups with the CAPS score as an additional covariate demonstrated that for the left ACC, adding the CAPS score as a covariate increased the number of voxels in cluster \((-9, -24, 36)\) and added a new significant cluster \((30, 54, 27)\) in the frontal area of the brain. For the right ACC, the statistical significance and the number of voxels increased in one cluster \((6, -27, 39)\) and an additional second cluster \((24, 57, 27)\) was found in the frontal area (Table 4). These findings indicate that the rs-fc group differences between the mTBI and no-TBI group remained significant after controlling for the CAPS scores, suggesting that the PTSD symptomology does not account for the rs-fc group differences between the mTBI and no-TBI group.

### 3.3. ACC regressions with TBI measures

To investigate the impact of TBI metrics as measured by the OSU-TBI scale on ACC connectivity, regressions were calculated with number of months since the most recent TBI and with number of months since the most severe TBI and ACC connectivity data in the mTBI group. After running multiple regression analysis (2 seeds x 2 clinical measures) and applying correction for multiple comparisons, there were no significant relationships between ACC connectivity and TBI measures.

### 4. Discussion

We investigated group level differences in ACC resting connectivity between Veterans who had sustained a mTBI in their lifetime and Veterans who reported they had never sustained a mTBI using a seed-based approach. We observed that the mTBI group exhibited stronger connectivity of the ACC with a number of brain regions including the precuneus, occipital, somatosensory, and middle and posterior cingulate regions. After controlling for the CAPS scores, the group differences in the rs-fc remained significant suggesting that the increased connectivity of the ACC in the mTBI group is not solely the consequence of higher CAPS scores in the mTBI group.

Our results are consistent with a previous report of increased ACC connectivity with frontal and parietal regions in concussed vs. non-concussed athletes in the absence of any group differences in neurocognitive results [45]. This study found that concussed subjects had significantly increased connections between areas of the brain that underlie executive function suggesting that even at rest, brains of concussed athletes may have to ‘work harder’ than their healthy peers to achieve similar neurocognitive results. Furthermore, Nathan and

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**Table 2**

Demographic and clinical variables. Values are depicted as mean (Standard Deviation).

|                  | mTBI       | Non-TBI    | p-value    |
|------------------|------------|------------|------------|
| Sex (% male)     | 89.7 %     | 65.3 %     | 0.0098 (chi-square) |
| Age              | 38 (9.1)   | 34.3 (9.2) | 0.11 (Mann-Whitney) |
| Education        | 15.1 (1.7) | 14.5 (2.4) | 0.07 (Mann-Whitney) |
| IQ               | 113.1 (9.4) | 110.0 (11.3) | 0.22 (Student’s \( t \)-test) |
| HAM-A            | 8.1 (7.3)  | 6.4 (6.7)  | 0.27 (Mann-Whitney) |
| HAM-D            | 7.1 (6.8)  | 7.0 (7.4)  | 0.73 (Mann-Whitney) |
| CAPS scores      | 65.8 (50.0) | 46.2 (42.1) | 0.26 (Mann-Whitney) |
| GAF scores       | 73.0 (15.4) | 76.6 (12.3) | 0.38 (Mann-Whitney) |
| PTSD diagnosis   | 20/49 (34.7 %) | 6/25 (20 %) | 0.15 (chi-square) |
| MDD diagnosis    | 18/49 (36.7 %) | 11/25 (44 %) | 0.54 (chi-square) |

GAF – Global Assessment of Functioning; HAM-A – Hamilton Anxiety Scale; HAM-D – Hamilton Depression Rating Scale; CAPS: Clinician-Administered PTSD Scale.

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**Table 3**

Resting state connectivity with seeds in left and right ACC for TBI and non-TBI groups (two-sample \( t \)-test with age, gender and education as covariates). The results were corrected for multiple comparisons using the AlphaSim program with a combined threshold of \( p < 0.03 \) and a minimum cluster size of 282 voxels for the FC with the left ACC and 315 voxels for FC with the right ACC.

|                  | \( p_{\text{FWE-corr}} \) | Cluster size | \( T_{\text{max}} \) | x    | y    | z    | Regions                                      |
|------------------|---------------------------|--------------|----------------------|------|------|------|----------------------------------------------|
| **SEED: Left ACC** |                           |              |                      |      |      |      |                                              |
| TBI > non-TBI    | <0.0001                   | 616          | 3.76                 | -9   | -24  | 36   | Cingulate_Post_R, Cingulate_Mid_L&R, SMA_L, Precuneus_R, Paracentral_Lobule_L&R, Cingulate_Ant_L, Cuneus_R |
| Non-TBI > TBI    | NS                        |              |                      |      |      |      |                                              |
| **SEED: Right ACC** |                          |              |                      |      |      |      |                                              |
| TBI > non-TBI    | 0.004                     | 383          | 3.26                 | -6   | -51  | 72   | Paracentral_Lobule_R, Precuneus_R, Cingulate_Mid_L&R, Cingulate_Post_R Occipital_Sup_L&R, Precuneus_L |
| Non-TBI > TBI    | 0.008                     | 346          | 3.22                 | 6    | -27  | 39   | Cingulate_Post_R, Cingulate_Mid_L&R, SMA_L, Paracentral_Lobule_L&R |
|                  | NS                        |              |                      |      |      |      |                                              |
colleagues reported an abnormal pattern of hyperconnectivity in the ACC as well as other brain regions when examining the DMN in mTBI participants 5 months after injury [22]. An increase in connectivity measured by temporal correlation between the precuneus and the ACC has also been previously reported in mTBI, which is consistent with our findings [46]. This study demonstrated alterations of multiple brain networks at the resting state, particularly increased functional connectivity in the frontal lobe, in response to brain concussion at the acute stage. However, there are also reports of reduced connectivity of the ACC in mTBI based on a study demonstrating that the early phase of

Fig. 2. Clusters of significant functional connectivity of the left ACC seed region in (A) TBI group and (B) no-TBI group, and of the right ACC seed region in (C) TBI group and (D) no-TBI group (one-sample t-tests, maps thresholded at $p < 0.05$, FWE corrected, cluster size >100 voxels). Results are displayed using MRicrGL and projected on MN152_2009 standard brain (University of South Carolina, Columbia, SC). Color bar represents t-values.

Fig. 3. Increased functional connectivity in TBI group compared to no-TBI group for the seeds placed in (A) left and (B) right ACC regions (two-sample t-tests, $p < 0.03$, AlphaSim cluster-extent corrected, cluster size > 282 voxels for the left ACC and cluster size >315 voxels for the right ACC). Results are displayed using MRicrGL and projected on MN152_2009 standard brain (University of South Carolina, Columbia, SC). Color bar represents t-values. The coordinates of the cluster’s maxima are listed in Table 3.
mTBI was characterized by a functional hypococonnectivity in a subnetwork with a large overlap of regions involved within the classical DMN [47].

Increased functional connectivity in mTBI could be due to diffuse impact on axons [48] or the microvasculature [49]. It has been suggested that functional hyperconnectivity may be a fundamental response to neurological disruption, which may be a paradoxical consequence to structural disruption [50]. For example, Nakamura and colleagues showed increased overall functional connectivity in participants with severe TBI, 3 months after injury as compared to healthy control participants, which was interpreted as a potential compensatory effect due to TBI [51]. Functional hyperconnectivity following injury is most commonly observed in hub regions [52], which are the most metabolically efficient nodes of a network that have unusually high connectivity to other nodes and high connectivity to other hubs [53]. Therefore, enhancing the connectivity in hub regions of the brain permits re-establishing network functioning while balancing cost-efficiency trade-offs [54]. The cost metric is based upon three important properties of the functional network: the number, strength, and physical length of functional connections, which determines the overall network efficiency. Cost-efficiency is defined as the trade-off between the metabolic demand of a network and the effectiveness of information transfer. Neuroimaging studies have identified the ACC, especially the rostral subdivision, as a hub of the brain’s network [55]. In network theory, hubs are nodes of a network that have unusually high connectivity to other nodes and high connectivity to other hubs. Thus, it is plausible that the observed hyperconnectivity of the ACC in Veterans with mTBI reflects a compensatory mechanism developed to maintain efficient network efficiency after injury. Since the ACC is a hub region, the cost associated with hyperconnectivity is low.

The ACC plays a crucial role in cognitive and emotional modulation, conflict monitoring, and social processing [56]. Therefore, alterations in ACC rs-fc can potentially result in disruptions in several emotional and cognitive domains. For example, increased ACC to precuneus rs-fc has been observed in Veterans with impulsive aggression and panic disorder [57]. The increased precuneus to ACC rs-fc may suggest increased vigilance and attention to internal visceral signals, which can be maladaptive [57]. The ACC to occipital lobe pathway is involved in visual recognition and believed to play a role in episodic memory [58]. It is possible that ACC hyperconnectivity may be associated with the post-concussive symptoms observed in TBI (such as cognitive complaints and sleep problems) or the hyperconnectivity is able to compensate for the structural damage in order to maintain normal neurocognitive performance. Longitudinal assessments of rs-fc as well as neurocognitive measures after mTBI in Veteran populations to better understand the dynamic changes in rs-fc as they relate to behavioral and cognitive changes are needed. The current study found no significant association between time since injury and ACC connectivity.

4.1. Strengths and limitations

The present study included a number of strengths and limitations that should be considered when interpreting the findings. TBI is an area of great importance in the health and treatment of Veterans and increasing the understanding of the mechanisms that underlie the pathophysiologic consequences of TBI is imperative. An important strength of this study is that comprehensive psychosocial interviews and assessment batteries were conducted in person by trained clinicians, and diagnostic assessments were derived via consensus. The completion of the OSU-TBI enabled use of standardized TBI definitions, including measures of severity of TBI and frequency of TBI. The current study findings are based on a sample that includes both male and female Veterans with a variety of comorbid health conditions allowing us to generalize these findings to a broader veteran population. Sex differences in orbitofrontal connectivity have been observed in Veterans with TBI and the inclusion of both male and female veteran participants will be important in understanding the impact of mTBI in the military [59].

Several limitations also need to be considered in interpreting this study data. First, a cross-sectional design as employed by the current study precludes any causal inferences. Longitudinal studies will be needed to assess the time-course of rs-fc changes and recovery after mTBI. Furthermore, a longitudinal study design can examine whether dynamic functional connectivity changes after mTBI may predict the prognosis and outcome of the disease. The second limitation is that the injuries that caused the mTBI in this study were heterogeneous resulting from blasts, falls, and accidents. Thus, we cannot identify the specific effects of different types of mTBI on rs-fc. It is highly likely that different types of TBI may exert divergent effects on neurobiological mechanisms given that the mechanics of the injury as well as the recovery profile are different. Third, the study was not able to control for some factors such as medication use and exposure to chronic stress, which may have an impact on the results. For example, there is evidence that antidepressants as well as chronic stress can alter functional connectivity [60]. Finally, the accuracy of self-reported data on TBI could have been affected by incorrect or incomplete recall, a problem endemic in most empirical research as well as clinical work in TBI.

5. Conclusions

This study showed that Veterans with mTBI in the chronic stage demonstrated increased rs-fc of the ACC with middle and posterior cingulate, occipital, somatosensory, and the precuneus as compared to Veterans with no TBI. These findings may reflect functional reorganization through compensation, neuronal plasticity or rerouting of functional connections in mTBI. As such the altered connectivity may be related to enhanced top-down control of attention networks necessary to compensate for the microstructural damage following mTBI.

CRediT authorship contribution statement

Chandni Sheth: Data curation, Formal analysis, Writing - original draft. Jadwiga Rogowska: Data curation, Formal analysis, Methodology. Margaret Legarreta: Supervision. Erin McGlade: Supervision. Deborah Yurgelun-Todd: Conceptualization, Funding acquisition,
Supervision, Project administration.

Declaration of Competing Interest

The authors report no declarations of interest.

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