DIFFERENCES IN BRAIN ARCHITECTURE DURING LONG-TERM RECOVERY FOLLOWING MILD TRAUMATIC BRAIN INJURY

BY

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THESIS

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ABSTRACT

Mild TBI (mTBI) is brain trauma from an external impact with a loss of consciousness less than 30 minutes. mTBI results in several biopsychosocial impairments with pronounced cognitive deficits, thought to resolve within three months of injury. Previous research suggests that these impairments are due to a temporary inability to appropriately allocate neural resources in response to cognitive demands. Our study questioned this assumption and instead hypothesized that mTBI was associated with *long-term* neural disruptions and compromised brain structure integrity. By extension, we investigated the likelihood that functional restitution and cognitive resolution following mTBI may be due to some form of neurofunctional reorganization. To this end, we examined abnormalities in resting state functional connectivity and structure (volume, thickness, and fractional anisotropy) in two groups of mTBI – those with 1-10 yrs. time-post injury ($mTBI_{1\text{-}10}$), and those with 20-65 yrs. time post-injury ($mTBI_{20\text{-}65}$), relative to age-, sex-, and education-matched controls. We observed abnormalities in brain architecture only in the $mTBI_{1\text{-}10}$ group, characterized by functional hypo-activation in the right frontal pole, smaller frontal pole volume, and lesser fractional anisotropy in the genu of the corpus callosum that extended near the right frontal pole. This frontal region is laterally specialized to regulate function specific to socio-emotional processes. Collectively, neural disruptions and structural insult in mTBI may persist up to 10 years following injury but injury-related pathology may resolve with longer recovery time. Disruption to frontal-dependent function that supports socio-emotional processes may also interfere with cognitive functioning, as in the case of chronic mTBI.

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CHAPTER 1: INTRODUCTION

The Neurotrauma Task Force of the World Health Organization describes traumatic brain injury (TBI) as an injury caused by mechanical forces to the head (e.g. injury due to falls, violence, being struck by an object). TBIs may be classified as mild, moderate or severe, depending on the extent to which an individual experiences loss of consciousness following the brain insult.[1] Although approximately 90% of all TBI individuals in the US are classified as mild TBI (mTBI), there is a relative dearth of biopsychosocial markers characterizing this segment of the population.[2-4] The apparent contradiction between mTBI prevalence and the restricted understanding of its causal mechanisms is due to operational elusiveness regarding its clinical-cognitive course towards functional stabilization. The present paper strives to address this problem by examining differences in brain architecture following long-term recovery in specific subsets of this population.

Whereas initial mTBI symptoms include cognitive impairments (such as problems in attention, memory, and executive functioning), a substantial portion of mTBI individuals show cognitive resolution—a return to pre-morbid levels of cognitive functioning within one to three months of injury. After cognitive resolution, these individuals perform as well as healthy controls on cognitive and behavioral assessments.[5,6] Typically, they do not show any overt neuropathology indicative of cognitive deficits. To explain this finding, Iverson et al.[7] have hypothesized that immediately after a brain insult, mTBI individuals experience a disruption in brain activity (e.g., decreased activity in prefrontal regions)[8] and related shifts in brain metabolism. However, their macroscopic morphology remains more or less intact. Consequently, structural neuroimaging does not show abnormalities in these populations.[5,9] This framework assumes that such injury-related neurological abnormalities are transient, and correspondingly,

that cognitive resolution parallels resolution of functional neural architecture[1] (*see also* World Health Organization's Operational Criteria for mTBI).[10]

This theoretical stance motivates much of the neuroimaging research, and as a result, brain analyses have been confined to exploring mTBIs up until the point of cognitive resolution, or shortly thereafter (also called acute-mTBIs). Corroborating this statement, a recent meta-analysis found that Fmri studies lacked predictive power towards providing an explanation of gross mechanisms of cerebral activity in mTBI.[8] This was mainly due to limited neuroimaging data in mTBIs following several years of injury, especially for resting-state. Collectively, it appears that a segment of the mTBI population, specifically those who reached cognitive resolution *and* sustained a contusion in their remote past (i.e. years ago), have been neglected from scientific investigation. We use "cognitively resolved remote mTBI" (CRR-mTBI) as a useful organizing term to characterize this mTBI subgroup.

The lack of research in CRR-mTBIs has made it difficult to explain why a fraction of the mTBI population (as many as 15% of adults and 40% of children)[1] continue to manifest symptoms at the chronic stage, with cognitive difficulties persisting even in the absence of conventional imaging evidence (e.g., CT scans, 3T MRIs). These shortcomings further compound the ambiguity towards operationalizing and assessing mTBI, to the extent that diagnostic evaluations can be largely subjective and prone to speculation.[11,12]

Taken together, it is unclear how the neuroarchitecture in CRR-mTBI changes over the course of time to parallel cognitive resolution. An examination of the individual differences in neuroarchitecture in CRR-mTBIs at different points of time post-injury could provide a roadmap for further investigation in this direction. Within this framework, it is possible that neurofunctional connections undergo *long-term* disruptions after brain injury, and new functional

relationships form to facilitate certain forms of cognitive resolution. By extension, functional restitution may not be related to the resolution of a temporary disability in managing cognitive demands, but due to some form of neurofunctional reorganization.[13] Thus, this conceptualization questions the *transient* nature of mTBI-related contusions advocated by some researchers (e.g. Morgan & Ricker)[1]. Bolstering this alternate perspective, a recent review cited a 6-week longitudinal study in which mTBI patients did not present with any performance deficits in a given working memory task (representing "cognitive-resolved mTBIs"). However, the participants demonstrated an increased neural activation in areas not related to working memory circuitry as a form of neurofunctional compensation.[14] Intriguingly, this compensatory activation was reduced in the follow-up session, indicating prolonged recovery that was only detectable in the functional activation of the injured brain.

Integrating these conceptualizations and related observations, the current study focuses on groups of CRR-mTBI individuals stratified across time post-injury. Given emerging evidence suggesting that age at concussion can affect long-term biopsychosocial outcomes in mTBI, we also chose to control for age-related confounds.[15] Accordingly, only individuals who had sustained an mTBI before 25 years of age were included in the study. Thus, we conducted analyses with CRR-mTBIs groups defined by time since injury, controlling for age at injury. The first group comprised individuals who suffered a concussion 1-10 yrs. Prior, hereafter referred to as the $mTBI_{1\text{-}10}$ group. The second group included individuals who suffered a concussion 20-65 yrs. Prior, hereafter referred to as the $mTBI_{20\text{-}65}$ group. Both groups were compared to age-, sex-, and education level- matched healthy controls, on a set of neuroimaging measures (i.e. $mTBI_{1\text{-}10}$ vs. controls and $mTBI_{20\text{-}65}$ vs. controls).

For both sets of comparisons, we explored the default mode network (DMN), a resting state network hypothesized to reflect internally-oriented cognitive processes such as mind-wandering, creativity, autobiographical, and prospective memory.[16] The DMN includes the ventromedial prefrontal cortex, rostral anterior cingulate cortex (Racc), posterior cingulate cortex (PCC), and the supramarginal gyrus (SMG). The Racc and PCC are considered the main "hubs" that promote integration by virtue of their long-range or varied connections,[17] with the cingulum bundle (a major white matter tract) connecting these anterior and posterior regions.[18] Decreased activity in the whole brain and the DMN immediately follow a TBI or mTBI.[18,19] Thus, we hypothesized that the healthy controls would show greater activation in this resting state compared to both post-injury groups, specifically in regions of the anterior cingulate, medial frontal gyrus, superior frontal gyrus, and anterior prefrontal cortex/frontal pole (*see meta-analysis by* Eirud et al.).[8] Our hypothesis rests on the premise that DMN-hypoactivation in mTBI can be detected even after recovery in cognitive outcomes.

Correspondingly, we tested for brain structural differences in the two mTBI groups relative to controls. Specifically, we tested for differences in morphometry (cortical thickness and volume) and white matter integrity (based on fractional anisotropy) obtained from diffusion-tensor imaging (DTI). DTI measures appear sensitive to the time since injury. A recent meta-analysis[8] demonstrated that frontal anisotropy was elevated in acute-mTBI (post-injury times less than 14 days), but depressed in chronic-mTBI (post-injury times greater than 14 days). Although these DTI studies did not track mTBIs following several years of injury, we speculated that DTI morphometry in our mTBI groups would resemble that of chronic-mTBI. Therefore, we predicted that the healthy controls would show greater anisotropy than the $mTBI_{1\text{-}10}$ group and the $mTBI_{20\text{-}65}$ group especially in the anterior regions of the brain.

In summary, a large body of mTBI literature assumes that cognitive-behavioral resolution in mTBI corresponds with neurocognitive-neurofunctional resolution. However, it is now known that a substantial number of mTBIs demonstrate persistent dysfunction, despite reaching apparent cognitive resolution. These findings suggest that equating cognitive resolution with neurofunctional restoration may not be accurate. Consequently, operationalization of mTBI is often subject to varied formulations and can severely undermine diagnostic judgments. Thus, there is an urgent need for studies that can provide a concrete understanding of the dynamics of neuroarchitecture in this population. Our study attempted to address this issue by examining two groups of CRR-mTBI individuals – those with 1-10 yrs. Time-post injury, and those with 20-65 yrs. Time post-injury. We compared both groups to healthy controls on measures of resting state activity, cortical thickness and volume, and fractional anisotropy values. Based on extant literature, we hypothesized that both mTBI groups would show hypo-activation in the default mode network, reduced cortical thickness and volume, and decreased fractional anisotropy especially in frontal brain regions.

CHAPTER 2: MATERIALS AND METHODS

2.1 PARTICIPANTS

Data from 44 right-handed participants were collected (mean age = 36.16, SD = 16.35) with informed consent. Information related to number of head injuries, approximate date, description of the event, and duration of symptoms (including duration of loss of consciousness (LOC) and post-traumatic amnesia) were obtained from all participants.

Individuals were assigned to the mTBI group if they met the following criteria: a diagnosis of mTBI by a medical professional and/or who had an LOC > 30 minutes and/or who had a post-traumatic amnesia <= 24 hours. This screening assigned 22 subjects to the mTBI group. Stratification was done by time since injury controlling for age at injury, leading to 12 mTBI participants falling under the 1-10 yr. category (i.e., $mTBI_{1\text{-}10}$). For comparison, 12 age-, sex-, and education-matched healthy controls were recruited. Ten mTBI participants were assigned to the 20-65 yr. category (i.e., $mTBI_{20\text{-}65}$). For comparison, 10 age, sex-, and education matched healthy controls were recruited. One control participant's imaging data from the $mTBI_{1\text{-}10}$ category was not available and therefore removed from all analyses (i.e., healthy controls N = 21; mTBI N = 22; total N = 43).

2.2 IMAGE ACQUISITION AND PROCESSING

All images were collected on a Siemens Trio 3-Tesla full body magnet, using a 12-channel birdcage head coil. Functional BOLD images were acquired parallel to the anterior commissure-posterior commissure (AC-PC) line with a T2-weighted echo-planar imaging sequence of 35 contiguous axial slices collected in ascending order [repetition time (TR) = 2000 ms; echo time

(TE) = 25 ms; BOLD volumes = 299; flip angle = 80◦; field of view (FOV) = 220×220mm; voxel size = 3.4×3.4×4mm]. Structural images were acquired with a T1-weighted 3D magnetization prepared rapid gradient echo imaging (MPRAGE) protocol of 192 contiguous sagittal slices collected in an ascending manner parallel to the AC-PC line [TR = 1900 ms; TE = 2.26 ms; flip angle = 9◦; FOV = 256×256mm; voxel size = 1×1×1 mm].

For each subject, two resting state scans were collected separately (2.5 minutes each). Image-processing was carried out with FSL version 5.0.4 (Functional Magnetic Resonance Imaging of the Brain's Software Library, http://www.fmrib.ox.ac.uk/fsl), AFNI,[20] and MATLAB (The MathWorks, Natick, MA, USA). Structural analysis was performed with FreeSurfer (http://surfer.nmr.mgh.harvard.edu).

The following processing steps were applied to each run: Raw DICOM images were converted to NIfTI format using FreeSurfer's *mri_convert* tool and reoriented to RPI orientation with FSL's *fslorient*. FSL's BET (Brain Extraction Technique) algorithm was then used to strip voxels containing non-brain tissue from the high-resolution T1 structural images.[21] Next, EPI data were motion corrected using AFNI's *3dvolreg* function, which produced six parameters of head motion. The motion-corrected EPI data were spatially smoothed using a FWHM 6.0 mm. gaussian kernel.

2.3 RESTING STATE

During resting state data collection, all participants were instructed to keep their eyes closed. The preprocessing steps for the resting state data were the same as those described above (see Image acquisition and preprocessing). In addition, single subject ICA was computed with FSL's MELODIC, an automated independent component analysis procedure that was used to generate

signal and noise components for each subject. Each component was visually inspected and manually classified as signal (components of interest) or noise (e.g., collection artifacts, signal of non-neural origin) by two independent raters based on recommendations by Kelly et al.[22]

To remove confounding signals such as those due to cardiac pulse, or low frequency scanner drift, the denoised images were bandpass filtered for frequencies below .008 Hz and above .1 Hz, using AFNI's *3dBandpass* tool. This band-pass filter was also applied to the 6 motion parameters mentioned above. The mean time series was then extracted from specific regions in deep white matter (retro-lenticular portion of the left internal capsule) and cerebrospinal fluid (left ventricle) and entered into the GLM as nuisance regressors (cf. Voss et al.).[23] The residual time series from this analysis for each run were concatenated and kept in native functional space for seed-correlational analysis.

Based on a previous study that explored functional connectivity in the mTBI population, we placed the seeds of the DMN within the rACC and PCC.[18] Voxel coordinates for each of these regions of interest (ROIs) matched those of Mayer et al.[18] (12mm spheres in the rACC [MNI 0, 49, 9], and PCC [MNI 0, -47, 33]). The following analyses were performed for each ROI. The ROI was transformed to each participant's native space. For every individual, we conducted a whole-brain functional connectivity analysis with the ROI, by extracting its mean time series and using Matlab to cross-correlate it with every other voxel in the brain. Cross-correlations were estimated as Pearson coefficients, which were then converted to subject-level Z-score maps using Fisher's r-to-z transformation. These whole-brain voxel-wise seed maps represented the co-fluctuations in amplitude of resting-state BOLD signal in each voxel and the target ROI.

At the group level, each participant's Z-map was first warped to MNI space [linear warp] and then all Z-maps were concatenated. The resultant image file was input to a between-subject ordinary least-squares (OLS) regression using FSL's *flameo*. Given our directional hypothesis that controls would show greater activation relative to both groups of mTBI, we identified two contrasts of interest. Our first contrast was the differential activation in the mTBI group with shorter time since injury (i.e., $mTBI_{1\text{-}10}$) relative to controls, which we labeled as "Control > $mTBI_{1\text{-}10}$". Our second contrast was the differential activation in the mTBI group with longer time since injury (i.e., $mTBI_{20\text{-}65}$) relative to controls, which we labeled as "Control > $mTBI_{20\text{-}65}$". Multiple comparisons were controlled by thresholding these contrast maps at $Z > 2.33$, with a cluster correction of $p < 0.05$. Regions that were observed to be differentially activated were saved as masks for further study (cf. Voss et al.).[23] We performed an ROI analysis using the generated masks for each participant (see below).

2.4 VOLUMETRIC AND THICKNESS-BASED MORPHOMETRY

FreeSurfer (surfer.nmr.mgh.harvard.edu, Version 5.3) was used to automatically compute volumetric and surface-based morphometric measures of the brain. For the surface measurements, each participant's cortical surface was extracted from their 3D high-resolution T1 MPRAGE image to create gray and white matter surface models separately for each hemisphere. These models were represented by a tessellated triangular mesh that had been inflated to a sphere and registered to a spherical atlas. The vertices (or nodes) of each triangle were assigned an index, and each index was further identified by a 2D (spherical) coordinate system. These indices were used to calculate various subject-level morphometric statistics such as cortical thickness,

surface area, sulcal depth, and gyral height as well as group-level comparisons on these measures. The Desikan-Killiany classification atlas was used to identify specific brain regions.

Volumetric measurements were estimated by segmenting the brain into white matter, gray matter, and cerebrospinal fluid. Segmentation was done using voxel-wise intensity differences and a probabilistic anatomical brain atlas. The voxel-based intensity statistics were then used to compute volumetric measures as a percentage of each participant's intracranial volume, thus controlling for variation in individual skull size. These measures included total gray matter volume, total white matter volume, and total brain volume across hemispheres as well as volumes for each structure labeled by the Desikan-Killiany atlas (*see* Trefler et al. for a more detailed overview).[24] Thickness and volume measurements were extracted from the ROI defined by a significant difference in DMN connectivity between both sets of comparisons.

2.5 FRACTIONAL ANISTROPY

The DTI data was preprocessed using the TORTOISE software (http://tortoisedti.nichd.nih.gov/). The TORTOISE module DTIPrep was used to perform image/diffusion information check, padding/cropping of data, slice-wise, interlace-wise and gradient-wise intensity and motion check, head motion and Eddy current artifact correction. The command DIFF_PREP was used to register the data to the subject's native structural space. DIFF_CALC was then used to process the tensor images, using a non-linear tensor fitting. The resulting TI images (specifically the fractional anisotropy images) were fed into FSL's TBSS software (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS) for statistical analysis.

CHAPTER 3: RESULTS

The age range of participants in the $mTBI_{1\text{-}10}$ group was 20-27 years; that of matched controls was 20-28 years. The age range of participants in the $mTBI_{20\text{-}65}$ group was 40-67 years; that of matched controls was 40-66 years. For a detailed description of participant demographics, please refer to Tables 1-2.

3.1 RESTING STATE

For the resting state DMN data, only the planned comparison for Control > $mTBI_{1\text{-}10}$ showed significant differences, and only for the seed placed in the PCC. Specifically, the PCC region in healthy controls showed significantly greater correlation with the right frontal pole/anterior prefrontal cortex relative to $mTBI_{1\text{-}10}$ ([36,54,18], peak z-value = 3.37, $p < 0.05$ cluster corrected; see Figure 1).

3.2 VOLUMETRIC AND THICKNESS-BASED MORPHOMETRY

A volumetric analysis showed significant thickness and volume deficits in the $mTBI_{1\text{-}10}$ group relative to controls, mainly in the superior frontal gyrus and frontal pole (both left and right hemispheres). However, these measures were not statistically significant for the target frontal pole region identified in the functional analysis (Table 3, Figures 2-3).

3.3 FRACTIONAL ANISTROPY

Comparing the diffusion coefficients for fractional anisotropy, our results only showed significant differences for the Control > $mTBI_{1\text{-}10}$ group. Specifically, we found significant

activation the body of the corpus callosum, extending to the right genu of the corpus callosum (Figure 4).

CHAPTER 4: DISCUSSION

Our study questioned the *transient* nature of mTBI-related contusions as advocated by some (e.g., Morgan & Ricker)[1] and we raised the possibility that concussions could result in *long-term* neural disruptions. By extension, we investigated the likelihood that neurofunctional restitution following mTBI may not be related to temporal disability to modulate processing resources in response to cognitive demands, but due to some form of neurofunctional reorganization.[13]

We found that in contrast to age-, sex-, and education-matched controls with absence of head trauma, there was decreased resting state functional activity in the 1-10 yr. post-injury mTBI group (i.e., $mTBI_{1\text{-}10}$) in the combined right frontal pole and anterior prefrontal cortex region. There were no differences in resting state functional activation for the 20-65-year post-injury mTBI group (i.e., $mTBI_{20\text{-}65}$) relative to healthy controls. These results suggest that functional abnormalities following concussion (that first occurred at the age of 25 years or younger) persist at least up to 10-years post-injury, but achieve functional normalization 20-65-years post-injury. That is, there are *long-term* functional disruptions after mTBI (continuing up to at least 10 years) in the right frontal region, with restoration of normal functional activity in this brain area following 20-65 years of mTBI.

Our observation that the right frontal pole is implicated in resting state functional connectivity in mTBI has been corroborated by Mayer et al.[18] for mTBIs following a few months on injury. Specifically, Mayer and colleagues found greater BOLD connectivity within this region (BAs 9/10) for controls compared to mTBI patients with head injuries within 3-5 months and normal neuropsychological results. Our structural analyses also supported the idea that the right frontal pole plays an important role in long-term recovery from mTBI, given that the

mTBI$_{1\text{-}10}$ group showed reductions in cortical thickness and volumes in this region and decreased anisotropy in the right genu of the corpus callosum. The right genu of the corpus callosum lies in close proximity to the right frontal pole. Taken together, these results suggest that deficits in functional activation and structural integrity in the right frontal region may be related.

One theory for why the right frontal pole is especially vulnerable to mTBI is based on observed morphological asymmetries in the frontal lobes. In the most typical configuration of the cerebral hemispheres in modern humans, the surface of the right frontal pole has a slightly greater protrusion than the left (*also known as the "Yakovlevian torque"*).[25,26] This anatomical asymmetry may make the right frontal pole more susceptible to concussions. Bolstering this theory, developmental studies have found that right frontal regions are particularly sensitive to brain injury in early childhood (cf. Levan et al.),[27] a period marked by critical maturation of the frontal lobes. Some have speculated that cognitive and behavioral issues that arise later in development may be traced back to these early injuries,[27] further raising questions regarding the transient nature of biopsychosocial sequelae immediately following mTBI. Along these lines, it is possible that the mTBI participants recruited in this study suffered their first concussion at a stage where their brains were still developing.

The frontal pole has been hypothesized to act as a "supervisory attentional control system".[28] In this role, the frontal pole regulates functional reorganization so that voluntary attentional demands are met.[28-30] Additionally, there is lateralization of brain function in this brain area. In particular, the right frontal pole is thought to regulate functional reorganization related to specific socioemotional processes such as perspective taking.[27,31] Thus, it is possible that persistent observed difficulties in mTBI are associated with pronounced impairments in these specific socioemotional processes. Additionally, neurofunctional reorganization related to

these socioemotional processes could interfere with cognitive functioning. This would explain why a fraction of the mTBI population continue to manifest cognitive problems at the chronic stage.

In sum, our results indicate that brain architectural changes in mTBI may be long-term and related to functional reorganization. Specifically, these long-term brain changes are associated with both structural and functional deficits in the right frontal pole. We theorize that these deficits relate to impairments in specific socio-emotional processes that may also interfere with cognitive functioning, as in the case of chronic mTBI.

4.1 STUDY LIMITATIONS

Although our study provides a general understanding of brain changes in mTBI over time, there were a few limitations that should be considered when interpreting the results reported here. First, we generated two groups of CRR-mTBIs by stratifying with respect to time since injury and controlling for age at injury. We recognize that these groups do not allow the examination of uniform brain changes over time, due to the cross-sectional design and the discontinuity over years between the 1-10-year and 20-65-year groups. Further, the intervals of time since injury for the two groups were not equal due to the convenience sample available. A second related consideration is the relatively smaller sample size (neuroimaging data was obtained for 12 mTBI individuals in the 1-10-year group with 11 matched controls, and 10 mTBI individuals in the 20-65-year group with 10 matched controls) that was due to restricted access to the mTBI population. Therefore, it is difficult to gauge the generalizability of our findings. Third, we did not investigate how differences in brain architecture may be related to cognitive-emotional functioning, thus limiting our ability to interpret the behavioral consequences of the long-term

injury to the frontal pole in mTBI. Future studies should examine how the right frontal pole is related to persistent difficulties in this population, using a larger sample size than was used in this study. Finally, a longitudinal study with long-term follow-up is necessary to determine recovery trajectories in mTBI and the degree to which changes in cognitive function are out-of-sync with changes in neurofunctional architecture.

CHAPTER 5: CONCLUSION

Our study was the first to examine neuroarchitectural change in mTBI following years of injury (see Eierud et al. for the limited number of resting state studies completed in this population).[8] We found that that structural and functional brain changes in mTBI are long-term, lasting up to 10-years post-injury. This finding contrasts with previous reports which suggest that mTBI-related neural changes are transient, and last only up to 3-months post-injury. Further, we found that these changes are primarily related to functional and structural deficits in the right frontal pole. Future studies should investigate how this region may explain socio-emotional functioning and its interaction with cognitive functioning in long-term mTBI.

CHAPTER 6: TABLES

Table 1: Participant demographics for 1-10 yrs. post-injury mTBI and matched controls

	1-10 yr. post-injury mTBI (n=12)			**Matched Controls (n=12)**		
PARAMETER	**Mean**	**Median**	**S.D.**	**Mean**	**Median**	**S.D.**
Age (yrs)	22.42	22.00	2.02	22.55	21.00	2.58
Gender (F)	7	-	-	7	-	-
Education (No. of Yrs.)	15.42	15	0.51	15.73	16	0.79
Time since first injury (yrs)	4.00	3.00	3.19	-	-	-
No. of concussions	1.25	1.00	0.62	-	-	-

Table 2: Participant demographics for 20-65 yrs. post-injury mTBI and matched controls

	20-65 yr. post-injury mTBI (n=10)			**Matched Controls (n=10)**		
PARAMETER	**Mean**	**Median**	**S.D.**	**Mean**	**Median**	**S.D.**
Age (yrs)	52.90	51.00	9.40	52.50	52.00	7.86
Gender (F)	4	-	-	4	-	-
Education (No. of Yrs.)	17.3	17	3.86	17.3	3.62	16
Time since first injury (yrs)	39.00	39.00	12.57	-	-	-
No. of concussions	1.40	1.00	0.52	-	-	-

Table 3: Thickness and Volume deficits in $mTBI_{1-10}$ relative to matched controls

Morphometric Measure	Hemisphere (L=Left, R=Right)	MNI Coordinates (Voxels)			Cluster Size (mm^2)	Brain Region
		X	Y	Z		
Thickness	L	48	78	61	562.33	Superior Frontal
		52	62	70	70.47	Superior Frontal
	R	37	91	27	108.09	Frontal Pole
Volume	L	62	89	31	140.22	Rostral Middle Frontal/Frontal Pole
		50	91	30	168.79	Frontal Pole
	R	38	92	28	79.14	Frontal Pole
		35	92	39	83.93	Rostral Middle Frontal/Frontal Pole
		26	89	33	91.67	Rostral Middle Frontal/Frontal Pole

CHAPTER 7: FIGURES

Figure 1: Functional connectivity differences with the PCC seed for Control > $mTBI_{1\text{-}10}$. Results depicted at $p < 0.05$, cluster corrected. Coordinates are voxels in MNI152 space.

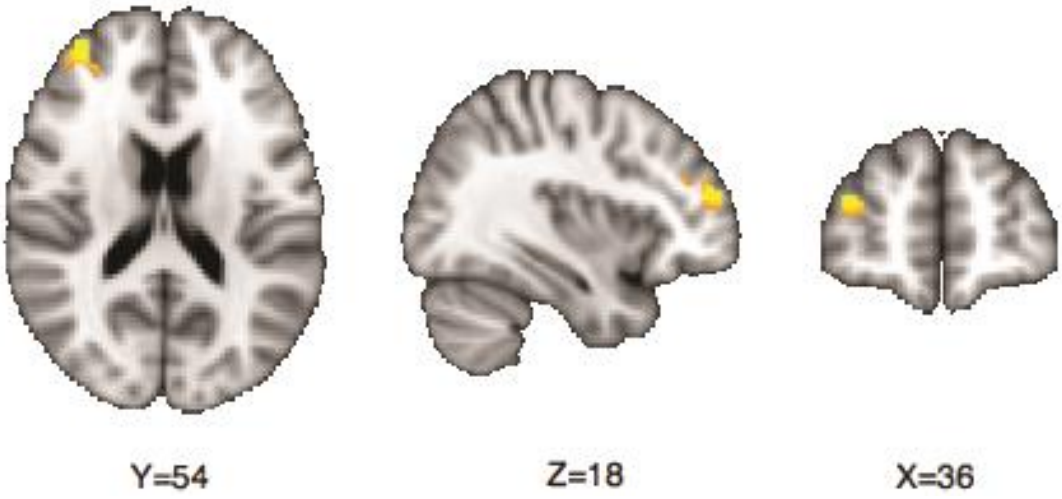


Figure 2: Volumetric deficits in the mTBI$_{1\text{-}10}$ group relative to controls within the fronto-polar cortex (FPC) and superior frontal gyrus. Results depicted at $p < 0.05$, cluster corrected.

Figure 3: (A) Right fronto-polar cortex (FPC) region that was differentially activated for Control > $mTBI_{1\text{-}10}$ in rest-state DMN. (B) Group comparisons within this ROI revealed no thickness or volumetric differences.

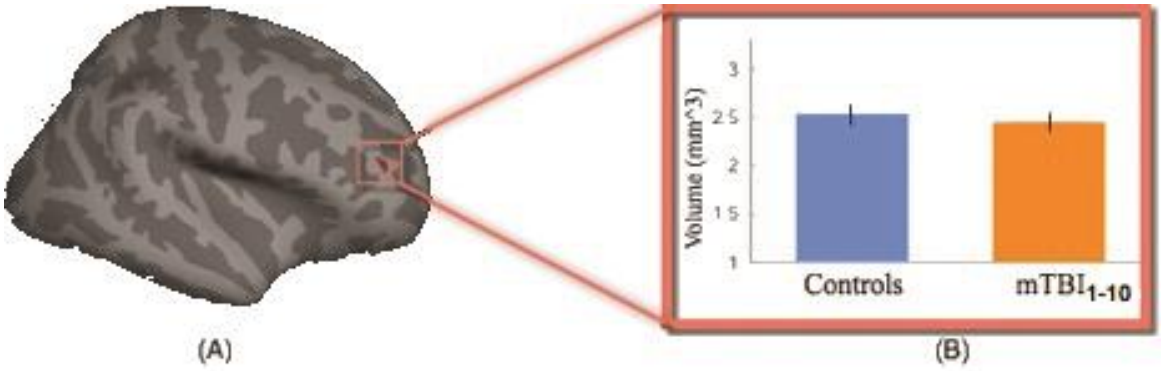
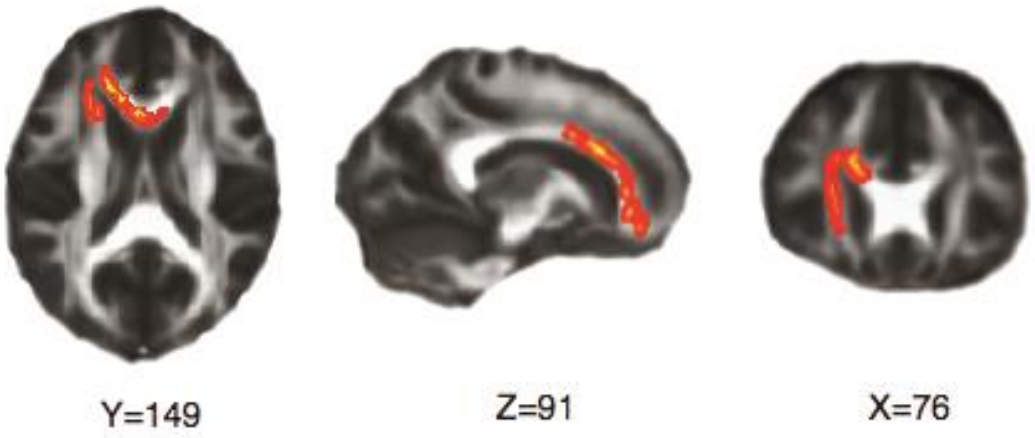


Figure 4: DTI anisotropy differences for Control > $mTBI_{1\text{-}10}$. Decreased anisotropy was observed in the body of the corpus callosum and in the right genu of the corpus callosum for 1-10 yr. post-injury mTBI relative to controls. Coordinates are voxels in MNI152 space.



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