Evidence Suggesting Prolonged Neuroinflammation in a Subset of Children after Moderate/Severe TBI: A UCLA RAPBI Study

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Abstract

Traumatic brain injury (TBI) presents a public health concern as a leading cause of death and disability in children. Pediatric populations are particularly vulnerable to adverse outcomes following TBI due to periods of rapid growth, synaptic pruning, and myelination. Pediatric patients with moderate-severe TBI (msTBI) and healthy controls were evaluated from the post-acute (2-5 months) to chronic phase (13-19 months) of recovery using diffusion magnetic resonance imaging (dMRI) and interhemispheric transfer time (IHTT), which is an event-related potential measure the speed of information transfer across the corpus callosum. We previously identified two subgroups of patients based on IHTT, with one group showing a significantly slower IHTT (TBI-slow), poorer cognitive performance, and progressive structural damage. In contrast, the other group (TBI-normal) did not differ from controls on IHTT or cognitive performance and showed relative structural recovery over time. Here, we examined group differences in restricted diffusion imaging (RDI), which is a dMRI metric sensitive to inflammation. Comparing TBI-slow, TBI-normal, and controls on RDI cross-sectionally, dMRI connectometry analysis revealed higher RDI across the white matter in the TBI-slow group compared to both the control and TBI-normal groups. Longitudinal analyses indicated that while both TBI groups exhibited a decrease in RDI over time, suggesting resolution of neuroinflammation and recovery, the decreases in the TBI-slow group were smaller. The differences in RDI between TBI-slow and TBI-normal suggest that inflammation may play a key role in the prolonged recovery, including brain structure, cognitive performance, and symptom reports, of pediatric patients with msTBI.

Introduction

Pediatric brain development is characterized by periods of rapid growth, synaptic pruning, and myelination.[1] Disruption during these processes may lead to long-term and severe consequences for cognitive, emotional, physical, and social function.[2,3] Traumatic brain injury (TBI) presents a significant public health concern as a leading cause of death and disability in children.[4] In 2019, there were over 60,000 TBI-related deaths in the United States, with children ages 0-17 accounting for approximately 4.1% of death. Additionally, in 2014, there were nearly 3 million TBI-related emergency department visits, of which 800,000 (~27%) were children between the ages of 0-17.[5] Children who sustain a moderate to severe TBI (msTBI) often experience long-term symptoms that can become more apparent as they enter critical periods of development, particularly with respect to cognitive and emotional functioning.[6,7] Cognitive impairments following TBI in pediatric populations can include deficits in attention, processing speed, memory, learning, emotional regulation, and executive functioning.[7–13] These changes are supported by neuroimaging findings, as pediatric patients frequently show corpus callosum lesions and other white matter disruptions, further indicating structural and/or functional disruption of the brain for a prolonged period following the initial injury.[14,15] There are several proposed mechanisms driving long-term disruptions: trauma or development during critical periods, altered neuroplasticity, impaired synaptogenesis, and prolonged inflammation.[16,17]

Regardless of the mechanism of brain injury, a consistent metabolic mechanism occurs in response to physical trauma. The brain experiences a cascade of chemical changes resulting in temporary disequilibrium, quantified by increased extracellular potassium levels which trigger excessive glutamate release. This release leads to the accumulation of intracellular calcium levels and ultimately results in mitochondrial respiration dysfunction, protease activation, and often apoptosis.[18–20] Secondary injury is the consequence of brain tissue damage and may occur minutes to months following the primary injury.[16,21] The specific mechanism of secondary injury is not clearly identified, but it is believed to play a key role in prolonged symptoms, particularly in pediatric patients.[4,7,16] Contributors to secondary injury include excitotoxicity, mitochondrial dysfunction, increased oxidative stress, weakened blood-brain barrier integrity, cerebral blood flow dysregulation, and inflammation.[16,22,23] In cases of chronic inflammation, the immune system remains in a heightened state, leading to glial cells having extended activation and a chronic pro-inflammatory response.[24] Animal models have repeatedly shown inflammatory markers such as leukocytes, pro-inflammatory cytokines, activated astrocytes, and microglia remain elevated 2-7 times longer in adolescent brains compared to adults, indicating this pathway could play a major role in prolonged recovery.[25,26,27] Adolescent mice with mild TBI show pro-inflammatory responses for 2 weeks post-injury, while only lasting 7 days in adults.[28] The contrast in recovery brings concern for development during critical periods and for long-term brain health, as chronic inflammation is often linked to neurodegeneration later in life.[16]

Measuring neuroinflammation *in vivo* is challenging, particularly outside of acute care settings and in pediatric populations. After hospital discharge, inflammatory markers can be measured through blood, but the relevance of these measures for inflammation in the brain is debated.[29–32] Positron emission

tomography (PET) can be used to detect activated microglia using TSPO tracers,[29] but PET is very rarely done in children because of radiation exposure. Ramlackhansingh et al. found evidence of elevated inflammation up to 10 years post-injury, and persistent inflammation was associated with poorer outcomes.[29] Advanced neuroimaging methods have great potential as biomarkers of injury and recovery. Diffusion magnetic resonance imaging (dMRI) is particularly promising given its sensitivity to white matter pathology, such as traumatic axonal injury (TAI).[33–35] TAI results from white matter bundles shearing and stretching during the injury, causing further tissue and cell damage. However, while dMRI can identify areas of disruption post-TBI, it has limited ability to determine the mechanisms of disruption. Lower fractional anisotropy (FA) is frequently reported[36–38] and can suggest demyelination, but can also indicate inflammation and changes in axonal packing.[39] Mean diffusivity (MD) can be used in TBI and other applications by identifying localized changes in water diffusion, and decreased MD can indicate cellular infiltration where inflammatory cells, such as macrophages, reduce the extracellular space for water diffusion.[40,41] However, MD can also indicate edema and fluid accumulation or other white matter changes in the brain unrelated to inflammation, though studies often report difficulties in relying on this metric.[42–46] Radial diffusion (RD) measures the diffusion of water perpendicular to the orientation of white matter fibers, and this metric is sensitive to changes in tissue integrity, specifically demyelination.[47,48] Axial diffusivity (AD) quantifies water diffusion parallel to the axonal tracts where lower AD generally indicates damaged or degraded axons; this degradation can become more pronounced due to inflammation or chronic diseases.[49,50] Restricted diffusion imaging (RDI) is a tensor-free and orientationally invariant metric used to quantify the total amount of restricted diffusion within a voxel, and RDI has been shown to correlate strongly with cell density.[51,52] Furthermore, several clinical trials have provided evidence that cell density is related to immune cell infiltration due to inflammation, supporting the use of RDI as a valuable metric that could potentially be more sensitive to neuropathology after TBI than traditional dMRI metrics (FA, MD, RD, AD).[53-54]

In a previous study, we identified two subgroups of pediatric msTBI patients with different post-injury trajectories.[55–59] Groups differed based on interhemispheric transfer time (IHTT), a visual evoked related potential (ERP) measure of the speed of information transfer across the corpus callosum and a marker of white matter integrity.[55,60,61] We found a bimodal distribution in the TBI group where patients with significantly slower IHTT showed poorer cognitive performance and more extensive abnormalities on neuroimaging when compared to TBI patients with normal IHTT. Analysis with whole brain magnetic resonance spectroscopy (MRS) found group differences in choline, a marker of inflammation and/or cellular turnover.[62] These results along with other evidence in the literature and the understanding that chronic inflammation is neurotoxic suggest that chronic inflammation may be present in some patients and may influence outcome. The TBI groups did not differ in demographic or early injury measures, but we hypothesized that chronic inflammation may play a role in their strikingly different trajectories. To test this, we extended our previous dMRI analyses in the same sample by examining RDI in the present analysis. For the current analysis, we hypothesize that children with msTBI in the slow IHTT range (TBI-slow) will show higher RDI cross-sectionally (i.e., more inflammation), and that this will be associated with

poorer cognitive performance. Further, we hypothesize that the TBI-normal group will show greater decreases in RDI longitudinally compared to TBI-slow.

Methods and Materials

Participants

TBI participants were recruited from four Pediatric Intensive Care Units (PICUs) located in Level 1 Trauma Centers in Los Angeles County. A study representative discussed the goals of the study with the parents of patients, gave them an IRB-approved brochure about the study, and obtained permission for the investigators to contact them after discharge from the PICU. Thirty-five percent of patients, whose parents agreed to be contacted while the child was in the PICU, participated in this study. Healthy controls, matched for age, sex, and educational level, were recruited from the community through flyers, magazines, and school postings.

Inclusion Criteria: 1) non-penetrating msTBI (intake or post-resuscitation Glasgow Coma Scale [GCS] score between 3 and 12 or GCS between 13-15 with positive image findings)[63] ; 2) 8-18 years of age at time of injury; 3) right-handed; 4) normal visual acuity or vision corrected with contact lenses/eyeglasses; and 5) English skills sufficient to understand instructions and be familiar with common words (the neuropsychological tests used in this study presume competence in English).

Exclusion Criteria: 1) history of neurological illness, such as prior msTBI, brain tumor, or severe seizures; 2) motor deficits that prevent the subject from being examined in an MRI scanner (e.g. spasms); 3) history of psychosis, ADHD, Tourette's Disorder, learning disability, intellectual disability, autism, or substance abuse. These conditions were identified by parental reports and are associated with cognitive impairments that might overlap with those caused by msTBI. Participants were also excluded if they had metal implants that prevented them from safely undergoing an MRI scan. The inclusion and exclusion criteria for the healthy controls were the same except for inclusion criterion #1.

We studied a total of 38 children with msTBI, 17 with longitudinal MRI data, 13 with MRI data from the post-acute phase only (2-5 months post-injury), and 8 with MRI data from the chronic phase only (13-19 months post-injury). We also studied a total of 49 healthy control children, 23 with longitudinal MRI data, 21 at the first time point only and 5 at the second time point only. Of the 38 children in the msTBI group, 15 had slow IHTT (TBI-slow), 15 had normal IHTT (TBI-normal), and 8 did not have IHTT data collected. Demographic data are summarized in **Table 1.** The injury mechanisms for our TBI group were as follows: 12 motor-vehicle accident (MVA) – pedestrian, 6 fall – skateboard, 5 MVA – passenger, 2 fall – scooter, 2 sport-related, 1 assault, 1 fall – skiing, 1 fall – ladder, and 8 uncategorized blunt head trauma. The demographic information (see Table 1) from our sample is consistent with existing epidemiological information on pediatric/adolescent msTBI, both in the male-to-female ratio and in the types of injury mechanisms (Keenan and Bratton, 2006). From the CT scan that participants received at the hospital, the prevalence of CT findings was as follows across the 32/38 participants for whom we had clinical CT data: increased intracranial pressure (21.9%), traumatic axonal injury (15.6%), subarachnoid hemorrhage (28.1%), ventricular hemorrhage (18.8%), epidural hematoma (37.5%), subdural hematoma (46.9%),

intracerebral hematoma (43.8%), contusions (37.5%), skull fracture – any (68.8%), depressed skull fracture (34.4%), non-depressed skull fracture (34.4%).

Scan Acquisition

Participants were scanned on 3T Siemens Trio MRI scanners with whole brain anatomical and 66-gradient diffusion MRI (dMRI). Diffusion-weighted images were acquired with the following acquisition parameters: GRAPPA mode; acceleration factor phase encoding=2; TR/TE=9500/87 ms; FOV=256x256mm; isotropic voxel size=2mm. 72 images were collected per subject: 8 b_0 and 64 diffusion-weighted (b=1000 s/mm^2). Details of the EEG/IHTT acquisition can be found in Ellis et al., 2016.[55]

Scan Comparison: Partway through the study, scanning moved from the UCLA Brain Mapping Center to the Staglin IMHRO Center for Cognitive Neuroscience, but imaging was performed using a scanner of the same model and with the same scan parameters. Extensive testing was conducted with volunteer and phantom data to ensure no bias was introduced with respect to the study design. Details may be found in Dennis et al., 2015.[56]

TBI Subgroups

We previously found a subgroup within the pediatric msTBI patient sample with slower IHTT, based on a visual ERP, which we used to measure the functional integrity of the corpus callosum.[55,56] In the first few months post-injury, some msTBI patients have significantly impaired callosal functional and structural integrity, and this affects cognitive performance. Moreover, these differences appear to be progressive, with one pediatric msTBI subgroup showing ongoing white matter disruption, while the other appears to begin to return to a healthy trajectory.[57,58] Importantly, the subgroup with impaired callosal function in our sample do not differ from the msTBI patients with normal callosal function in demographic or acute injury variables. In all analyses on this dataset, we have examined the msTBI group as two groups – TBI-slow (those with significantly longer IHTTs) and TBI-normal (those with IHTTs in the normal range). The attrition rate did not differ significantly between TBI-slow and TBI-normal groups. In both the post-acute (n=4) and chronic (n=7) phases, there were TBI subjects we did not obtain IHTT data from but were included for other analyses.

dMRI Processing

dMRI volumes were denoised using local PCA denoising with Rician bias correction (LPCA[64]). Denoised volumes were eddy corrected using FSL 6.0 *eddy_openmp*. dMRI processing was performed using DSI Studio ("Chen" version, 2023.07.06 build on Mac; https://dsi-studio.labsolver.org/). All diffusion data were reconstructed in the MNI space using *q*-space diffeomorphic registration (QSDR)[65] to obtain the spin distribution function[66] with a diffusion sampling length ratio of 1.25. Restricted diffusion was quantified using restricted diffusion imaging.[52] Following reconstruction, longitudinal data for all participants were compiled into a dMRI connectometry database (N=129 scans).

dMRI Connectometry Analyses

Initial analyses were conducted within DSI Studio, with follow-up analyses conducted in R 4.4.1. Our primary measure of interest was RDI;[52] however, as prior studies have focused on more traditional tensor-based dMRI metrics, such as FA, MD, RD, AD we also examined these in the supplement for completeness, and these supplemental analyses are treated as *post hoc* comparisons. dMRI connectometry was used to derive correlational tractography for each dMRI metric tested.[67] A nonparametric partial Spearman correlation was used to assess the relationship with each metric between groups, with age and sex as covariates. A *T*-score threshold of 2.5 was applied with a length threshold of 15mm, and a deterministic fiber tracking algorithm was used to obtain correlational tractography.[68] The whole brain was seeded with 1,000,000 seeds, and topology-informed pruning was used to filter the tracts with 16 iterations.[69] A false discovery rate (FDR) threshold of q=.05 was used to select tracts.[69] Permutation testing with 4,000 permutations was used to estimate the null distribution.

Cognitive Performance

In our prior papers, we computed a summary measure of cognitive performance from tests assessing multiple domains known to be affected by TBI.[2] It is a linear, unit-weighted combination of the following age-based standardized measures: 1) Processing Speed Index from the WISC-IV/WAIS-III; 2) Working Memory Index from the WISC-IV/WAIS-III; 3) Trials 1-5 from the CVLT-C/II;[70] and 4) Trails Condition 4 from the D-KEFS.[71] Further details of our cognitive performance index (CPI) are found in Moran et al., 2016.[72] A higher summary score indicates higher cognitive functioning, whereas a lower summary score indicates lower cognitive functioning. In our prior papers, the two TBI subgroups differed on this summary measure of cognitive performance, with the TBI-slow group demonstrating poorer performance in the post-acute phase.

Statistical Analyses

Our primary analyses compared along-tract RDI between TBI-slow, TBI-normal, and healthy controls in three separate cross-sectional comparisons at each time point.

Additionally, we used correlational tractography to further examine associations between along-tract RDI and CPI, and we assessed the ability of post-acute RDI to predict CPI scores at the chronic time point.

Supplementary DTI Analyses

As DTI analyses were previously published,[57] we performed the same analyses as described above on FA, MD, AD, and RD, but these are included as post-hoc analyses in the supplemental material to enable comparisons between traditional tensor-based metrics and QSDR-derived RDI.

Results

As referenced above, the TBI-slow and TBI-normal groups were kept separate for all analyses. IHTT was measured at the post-acute phase and this grouping was used to examine RDI differences in both timepoints.

Cross-sectional comparisons

Post-acute Phase: TBI-normal vs. control: There were no significant differences in RDI between the TBI-normal (n = 13) and control (n = 28) groups at the post-acute phase. TBI-slow vs. control: Widespread differences in RDI were observed between the TBI-slow (n =14) and control (n = 28) groups at the post-acute phase, where RDI was significantly higher in the TBI-slow group (**Figure 1**). TBI-slow vs. TBI-normal: There were no significant differences in RDI between the TBI-slow (n = 14) and TBI-normal (n = 13) groups at the post-acute phase.

Chronic Phase: TBI-normal vs. control: Correlational tractography analysis revealed several tracts with significantly lower RDI in the TBI-normal (n = 9) group compared to controls (control n = 21) (**Figure 2**). TBI-slow vs. control: At the chronic phase, significantly higher RDI was observed in the TBI-slow (n = 10) group compared to controls (n = 21) (**Supplementary Figure 1**). TBI-slow vs. TBI-normal: Significantly higher RDI was observed across widespread white matter regions in the TBI-slow (n = 10) group compared to the TBI-normal (n = 9) group at the chronic phase (**Figure 4**).

Longitudinal comparisons

RDI similarly decreased on average in both the control and TBI-normal groups, whereas an overall increase in RDI was observed in the TBI-slow group (**Figure 5**).

Cognitive Performance

Our analysis of associations between RDI and CPI revealed widespread regions of white matter where higher RDI was significantly associated with lower CPI, in the post-acute phase, both across the full sample and within the TBI group only (n=72 & n=27, **Figure 6**). In the chronic phase, however, RDI was *positively* associated with CPI.

Supplementary DTI Analyses

Supplementary analyses were consistent with prior papers[56,57] and are shown in Supplementary Figures 1-3. *Post-acute:* We found significant differences between TBI-normal and control in one direction for AD, MD, RD, and RDI and significant differences in both directions for FA. We found significant differences between TBI-slow vs control in one direction for MD, RD, and RDI and significant differences in both directions for AD and FA. We found significant differences between TBI-normal vs TBI-slow in one direction for AD, RD, and RDI; both directions for MD; and no significant difference for FA. *Chronic:* We found significant differences between TBI-normal vs control in one direction for MD, RD, and RDI and significant differences in both directions for AD and FA. We found significant differences between TBI-slow vs control in one direction for all metrics. We found significant differences between TBI-normal vs TBI-slow in one direction for AD, FA, RD, and RDI and significant differences in both directions for MD. Regions with different MRI metric findings are shown at both time points in supplementary figures.

Discussion

This paper expanded on a previous project that identified two groups of children who incurred msTBI with different post-TBI trajectories.[38,57,73,74] In this study, we present evidence to suggest that there may be chronic neuroinflammation in a subset of pediatric patients after msTBI, and that this may be linked to poorer cognitive performance post-acutely. Specifically, we used IHTT to measure corpus callosum functioning – a structure that supports a large number of cognitive functions and is often disrupted in TBI. Children with msTBI who had slower IHTT in the post-acute phase showed higher RDI both in the post-acute and chronic phase compared to children with msTBI and IHTT times in the normal range, supporting our hypothesis. It is unclear why these two groups diverge in their recoveries, as other possible confounding variables have been accounted for (e.g. age, severity, acute neuropathology, SES); however, one leading hypothesis is prolonged neuroinflammation in the TBI-slow group may contribute to the observed differences.

The pediatric brain can respond differently to TBI than adult brains due to increased synaptogenesis, continuing myelination, and critical periods of development, among other factors.[16,75] In response to the primary injury of damaged neuronal tracts, a secondary response occurs including activating surrounding microglia, chemical pathways, and astrocyte movements in an inflammatory response.[76–78] Following TBI, several other inflammatory responses occur, including the penetration of the blood-brain barrier by neutrophils, T-cells, and monocytes and the production of antibodies to cerebral antigens by B-cells.[16,79] RDI is a non-invasive neuroimaging metric that is correlated with cell density due to immune cell infiltration, thus providing an indirect measure of neuroinflammation.[52] If inflammation is an underlying mechanism contributing to the divergence between these two msTBI subgroups in children, this could indicate potential clinical targets and suggest an expanded window for intervention beyond the acute phase. Additionally, RDI could be a promising diagnostic tool for children that avoids invasive techniques, such as lumbar puncture measuring inflammatory biomarkers or pharmacokinetic PET, which involves low levels of radiation exposure to detect activated microglia.[29] In the chronic phase, the TBI-normal group had significantly lower RDI than the healthy controls. With limited studies on RDI in humans and none focused on development, the reasons and implications for this are unknown. Lower RDI could be due to neuroplasticity as brain networks reorganize after injury, resolution of secondary injury mechanisms such as inflammation, post-injury remyelination, cell death, or breakdown of the extracellular matrix. RDI likely reflects different neurobiological processes at different times post-injury, so we hope that our work encourages other researchers to examine RDI in their datasets as well to give a fuller picture of the implications and potential of RDI.

We found that higher RDI was associated with lower cognitive performance in the post-acute phase, mirroring our prior papers identifying group differences in WM organization and summary cognitive performance at this time point. Rehabilitation methods in pediatric msTBI have targeted working memory as a key focus of overall cognitive improvement, supporting our findings of digit span as a useful biomarker and possible clinical measure.[80–82] Other studies in pediatric msTBI continually note that cognitive impairments following the injury, including worsened working memory, attention, and memory,

lead to long-term deficits in daily functioning.[83–85] The inconsistent associations between RDI and cognitive function require additional information to fully understand. It is possible, given that RDI is mathematically approximating a biological phenomenon, that RDI is reflecting different neuropathological processes at different stages post-injury. Our prior work demonstrated that these two groups of patients differ in longitudinal trajectories of structural development[56,57] but were unable to identify a causal factor. The present study expanded by evaluating differences in the TBI subgroups, and the changes in RDI show a correlation with worsened overall outcome, cognitive performance, and support the hypothesis that inflammation is the driving mechanism between these two groups. While RDI is still an indirect measure of inflammation, the present results bring us one step closer to understanding this divergence and, thus, hopefully one step closer to identifying new opportunities for intervention.

One limitation of this study is that RDI does not directly measure inflammation in the same mechanism as a blood biomarker or other invasive measure. Direct measures of neuroinflammation are difficult to collect, especially in pediatric patients and especially outside of the acute care context. Blood samples can reflect circulating inflammatory markers, but there is debate as to how well these peripheral markers correspond with neuroinflammation.[86–89] It is possible to collect cerebrospinal fluid during acute neurosurgery when placement of a shunt is necessary or through a lumbar puncture – this method allows for direct collection of central nervous system biomarkers indicative of inflammation. PK PET is a more direct imaging measure of inflammation, but this is more costly than MRI and far less common in pediatric studies and preclinical pathological correlation partly due to the radiation exposure. Still, these methods are not feasible nor ethical beyond the acute phase. Although RDI is not a direct measure, it has been validated with *in vivo* data, and the restricted interference can reflect the level of inflammation in a given area of the brain.[52,90,91] Another limitation is that RDI is more reliable in multi-shell diffusion acquisitions, and our acquisition only included a single diffusion weighting. Finally, we had a relatively small sample size with 39 TBI patients, albeit smaller with the subgroups, although this is in line with other publications. The lack of power for the analyses with subgroups and for longitudinal data may explain the inconsistent associations between RDI and cognitive function. RDI is a new metric with limited information in TBI and in pediatric populations, so additional future information will aid in the interpretation and whether it has prognostic benefits.

Here, we present evidence suggesting that a subset of pediatric msTBI patients have prolonged neuroinflammation and that these differences may contribute to cognitive deficits and slower recovery after injury. Previous studies indicate that RDI is more accurate in identifying inflammation than other commonly used MRI metrics.[52]. In this study, we demonstrate that RDI is more sensitive to changes in the chronic phase between TBI-slow and TBI-normal groups; this sensitivity is critical in identifying alterations in the brain following a TBI and the underlying mechanisms that lead to different trajectories of recovery in some patients. Though FA and MD have largely been used to identify TBI, RDI may be a more accurate diagnostic to identify and predict TBI recovery. Further studies in larger samples and/or including blood biomarkers of inflammation are needed to validate our results. Confirmation of our findings could suggest mechanistic clinical targets addressing neuroinflammation and potentially expanded windows of

opportunity for therapeutic intervention. Furthermore, utilizing RDI as a non-invasive diagnostic measure to identify the trajectory of pediatric msTBI may provide benefits both in identifying short- and long-term treatments while reducing the reliance on subjective reports, radiation exposure, and invasive measures.

Conflicts of Interest

The authors have no competing financial interests.

Acknowledgements

This study was supported by the NICHDS (R01 HD061504). ELD is supported by a grant from the NINDS (R01 NS122184). CCG is supported by the UCLA BIRC, NS027544, NS05489, UCLA Steve Tisch BrainSPORT Program and Easton Foundation. Scanning was supported by the Staglin IMHRO Center for Cognitive Neuroscience. We gratefully acknowledge the contributions of Alma Martinez and Alma Ramirez in assisting with participant recruitment and study coordination. Finally, the authors thank the participants and their families for contributing their time to this study.

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Figure and Table Legends

Table 1. Demographic information. Summarized demographic information, including age, sex, socioeconomic status, and time since injury, of TBI and control groups in the post-acute and chronic phase.

Figure 1. Post-acute differences in RDI between the TBI-slow and control groups. Tracts showing significantly higher RDI in the TBI-slow group in the post-acute phase are shown. Colors correspond to *t*-statistics as shown in the color bar. Right in image is left in brain. Video: https://drive.google.com/file/d/1iXUwQ1QYa5iV9n6OfhSERSbN-LkirF1l/view?usp=drive_link

Figure 2. Chronic differences in RDI between the TBI-normal and control groups. Tracts showing significantly lower RDI in the TBI-normal group in the chronic phase are shown. Colors correspond to *t*-statistics as shown in the color bar. Right in image is left in brain. Video: https://drive.google.com/file/d/11STaIwpu-rDZe-shQO7xYsQK0KeXZCBG/view?usp=drive_link

Figure 3. Chronic differences in RDI between the TBI-slow and control groups. Tracts showing significantly higher RDI in the TBI-slow group in the chronic phase are shown. Colors correspond to *t*-statistics as shown in the color bar. Right in image is left in brain. Video: https://drive.google.com/file/d/1BXS1YBhofSs8Cjid_5Vy3Sf_qrlTnKep/view?usp=drive_link

Figure 4. Chronic differences in RDI between the TBI-slow and TBI-normal groups. Tracts showing significantly higher RDI in the TBI-slow group compared to the TBI-normal group in the chronic phase are shown. Colors correspond to *t*-statistics as shown in the color bar. Right in image is left in the brain. Video: https://drive.google.com/file/d/1Rom_JmzgdaBOxNeOQKkBknbNcpbTRFsX/view?usp=drive_link

Figure 5. Associations between RDI and Summary cognitive scores during post-acute phase. Areas in blue are regions where lower cognitive function was associated with higher RDI. Right in image is left in the brain.

Figure 6. Associations between RDI and Cognitive Function. Along-tract negative associations between post-acute RDI and post-acute CPI in the TBI group. Colors correspond to *t*-statistics as shown in the color bar. Right in image is left in the brain. Right in image is right in the brain. Video: https://drive.google.com/drive/folders/191JGtHm5Oi5Lgnuix0ZqXHUyJ6VJ_roo

Table 1. Demographic information. Summarized demographic information, including age, sex, socioeconomic status (measured with highest parent education), time since injury, and acute neuropathology of TBI and control groups in the post-acute and chronic phase. TAI=traumatic axonal injury, H=hematoma or hemorrhage (subarachnoid, intraventricular, epidural, or subdural), C=contusion, SFx (skull fracture). 1 participant in the post-acute TBI-normal group and 1 in the chronic TBI group without IHTT data did not have an acute neuropathology report.

	Group	Age	Male	Female	IHTT [ms]	Highest Parent Education [Years]	TSI [weeks]	GCS	TAI | H | C | SFx
Post-acute	TBI-slow	13.7 (2.3)	9	5	26.2 (6.2)**	12.7 (3.8)	12.0 (4.8)	9.8 (4.0)	1 | 11 | 6 | 10
	TBI-normal	14.8 (3.0)	9	4	8.3 (5.4)	14.3 (4.0)	14.0 (5.1)	7.7 (3.9)	3 | 10 | 2 | 9
	TBI (No IHTT Data)	14.5	3	1	N/A	10.7 (1.9)	19.0 (7.3)	10.0 (2.8)	1 | 3 | 3 | 3
	Control	15.1 (2.8)	21	23	9.2 (5.6)	14.7 (3.7)	N/A	N/A	N/A
Chronic	TBI-slow	15.2 (1.9)	8	2	26.2 (6.3)**	13.1 (4.1)	62.0 (5.2)	8.2 (3.2)	1 | 8 | 5 | 7
	TBI-normal	16.9 (2.8)	7	2	8.2 (5.7)	15.2 (3.6)	64.7 (8.1)	10.3 (3.5)	0 | 7 | 3 | 5
	TBI (No IHTT Data)	16.9 (1.8)	6	1	N/A	13.6 (3.4)	61.9 (18.2)	9.7 (3.0)	2 | 5 | 3 | 3
	Control	16.8 (2.7)	18	10	10.2 (5.0)	15.7 (3.0)	N/A	N/A	N/A

** = < 0.01 significance
* = < 0.05 significance

** TBI-normal and TBI-slow IHTT in post-acute and chronic phases

Figure 1. Post-acute differences in RDI between the TBI-slow and control groups. Tracts showing significantly higher RDI in the TBI-slow group compared to the control group in the post-acute phase are shown. Colors correspond to *t*-statistics as shown in the color bar. Right in image is right in brain. Video: https://drive.google.com/file/d/1iXUwQ1QYa5iV9n6OfhSERSbN-LkirF1l/view?usp=drive_link

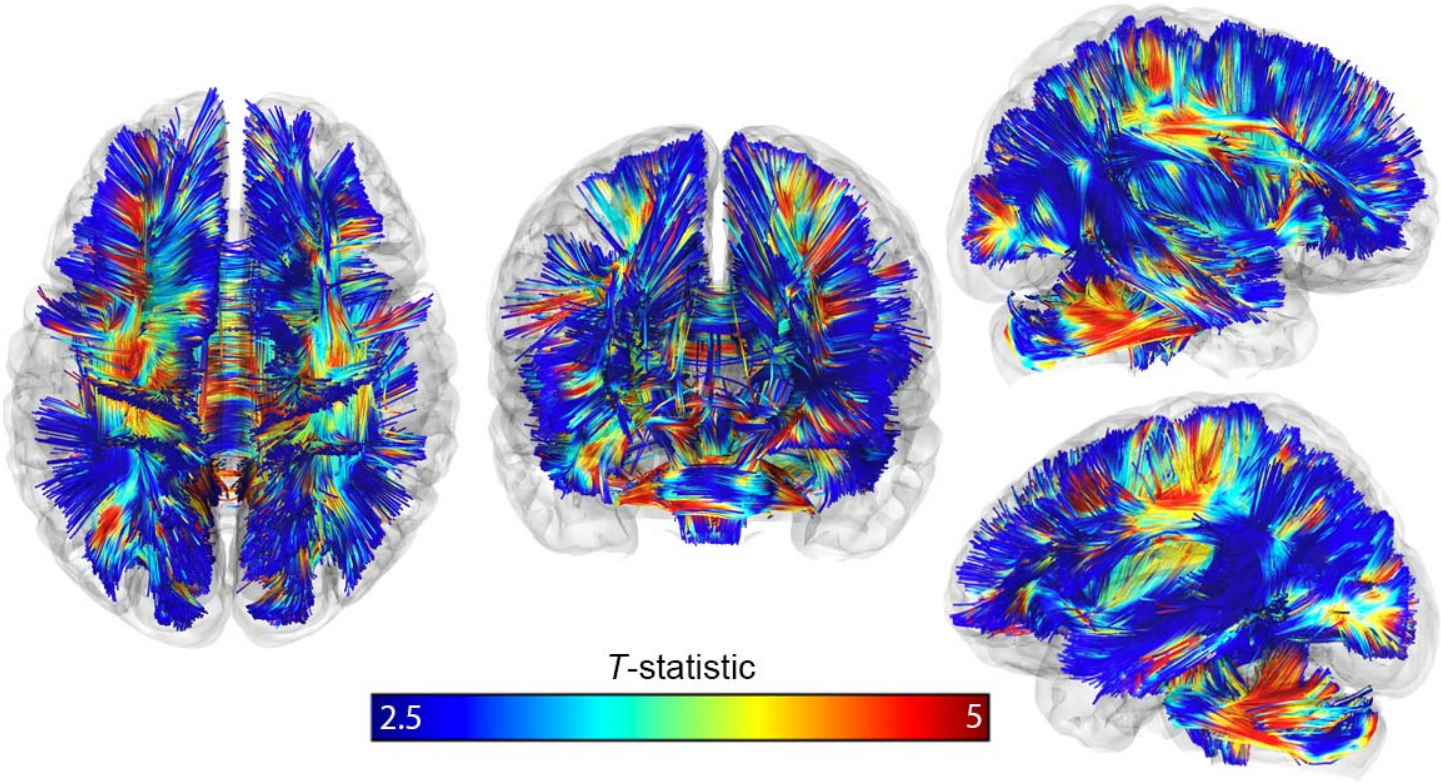

Figure 2. Chronic differences in RDI between the TBI-normal and control groups. Tracts showing significantly lower RDI in the TBI-normal group compared to the control group in the chronic phase are shown. Colors correspond to *t*-statistics as shown in the color bar. Right in image is right in brain. Video: https://drive.google.com/file/d/11STaIwpu-rDZe-shQO7xYsQK0KeXZCBG/view?usp=drive_link

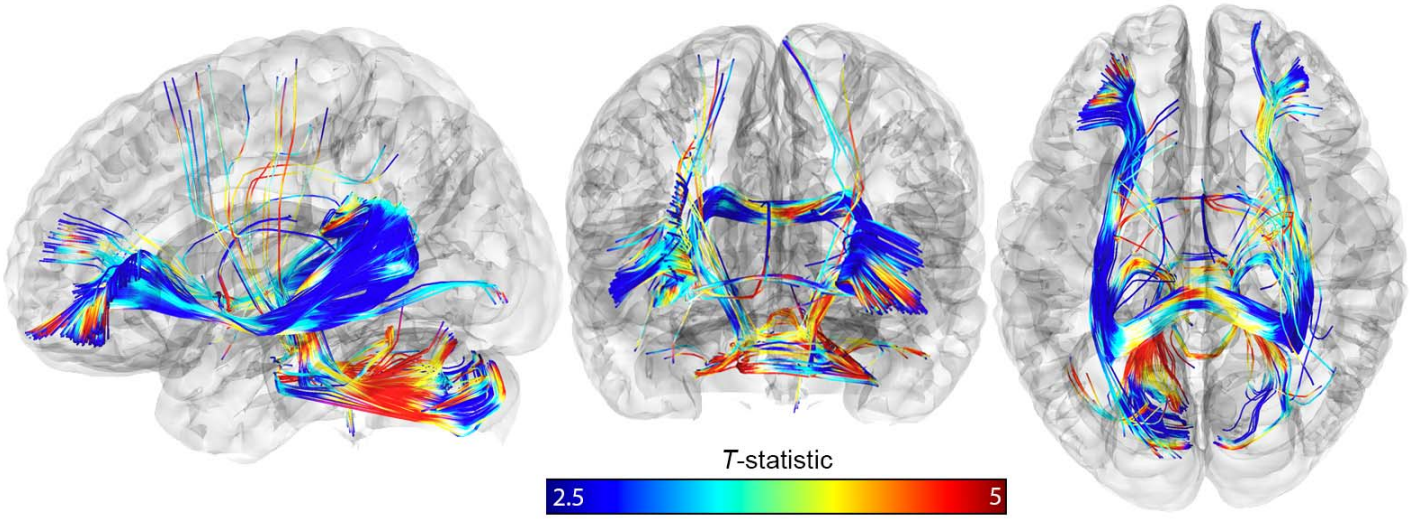

Figure 3. Chronic differences in RDI between the TBI-slow and control groups. Tracts showing significantly higher RDI in the TBI-slow group compared to the control group in the chronic phase are shown. Colors correspond to *t*-statistics as shown in the color bar. Right in image is right in brain. Video: https://drive.google.com/file/d/1BXS1YBhofSs8Cjid_5Vy3Sf_qrlTnKep/view?usp=drive_link

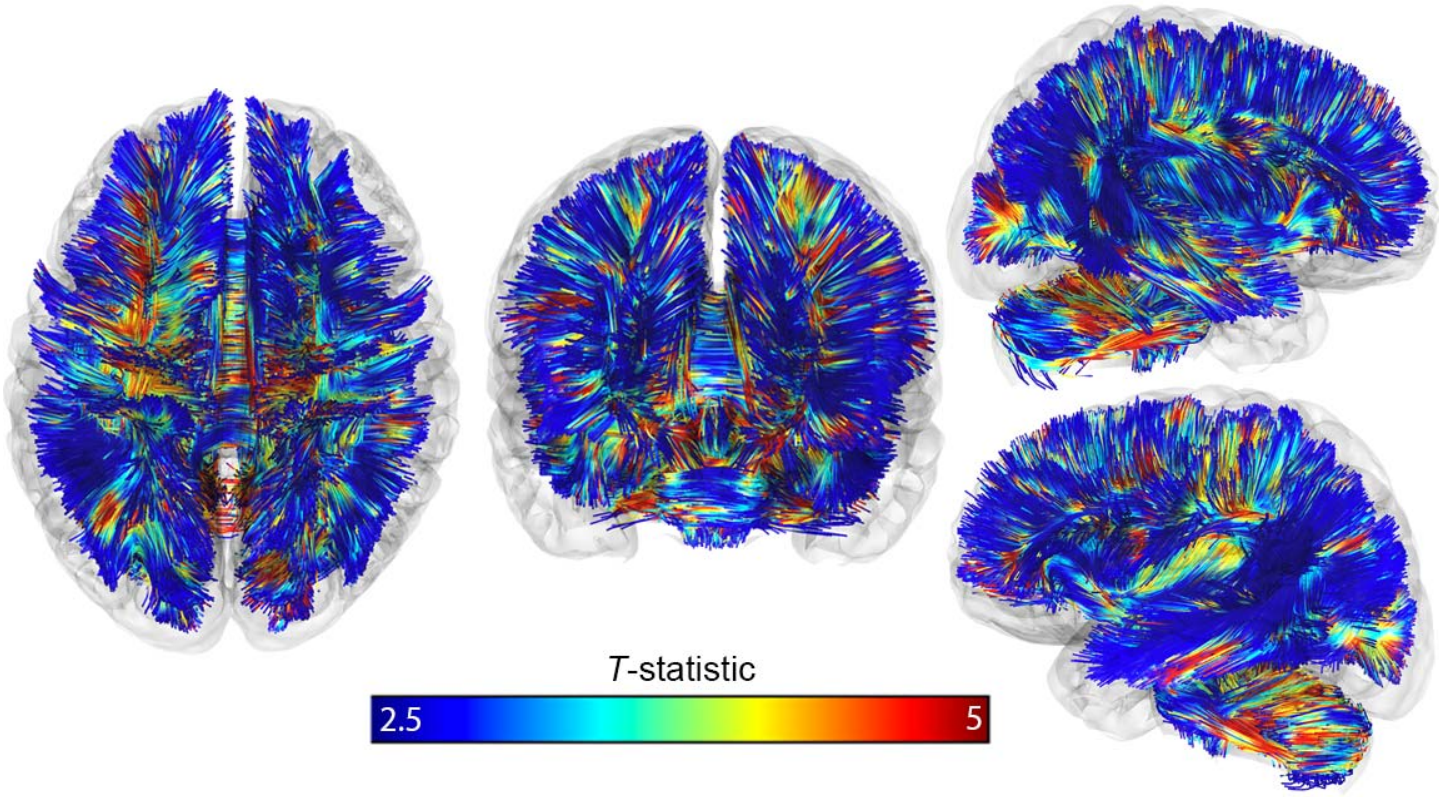

Figure 4. Chronic differences in RDI between the TBI-slow and TBI-normal groups. Tracts showing significantly higher RDI in the TBI-slow group compared to the TBI-normal group in the chronic phase are shown. Colors correspond to *t*-statistics as shown in the color bar. Right in image is right in the brain. Video: https://drive.google.com/file/d/1Rom_JmzgdaBOxNeOQKkBknbNcpbTRFsX/view?usp=drive_link

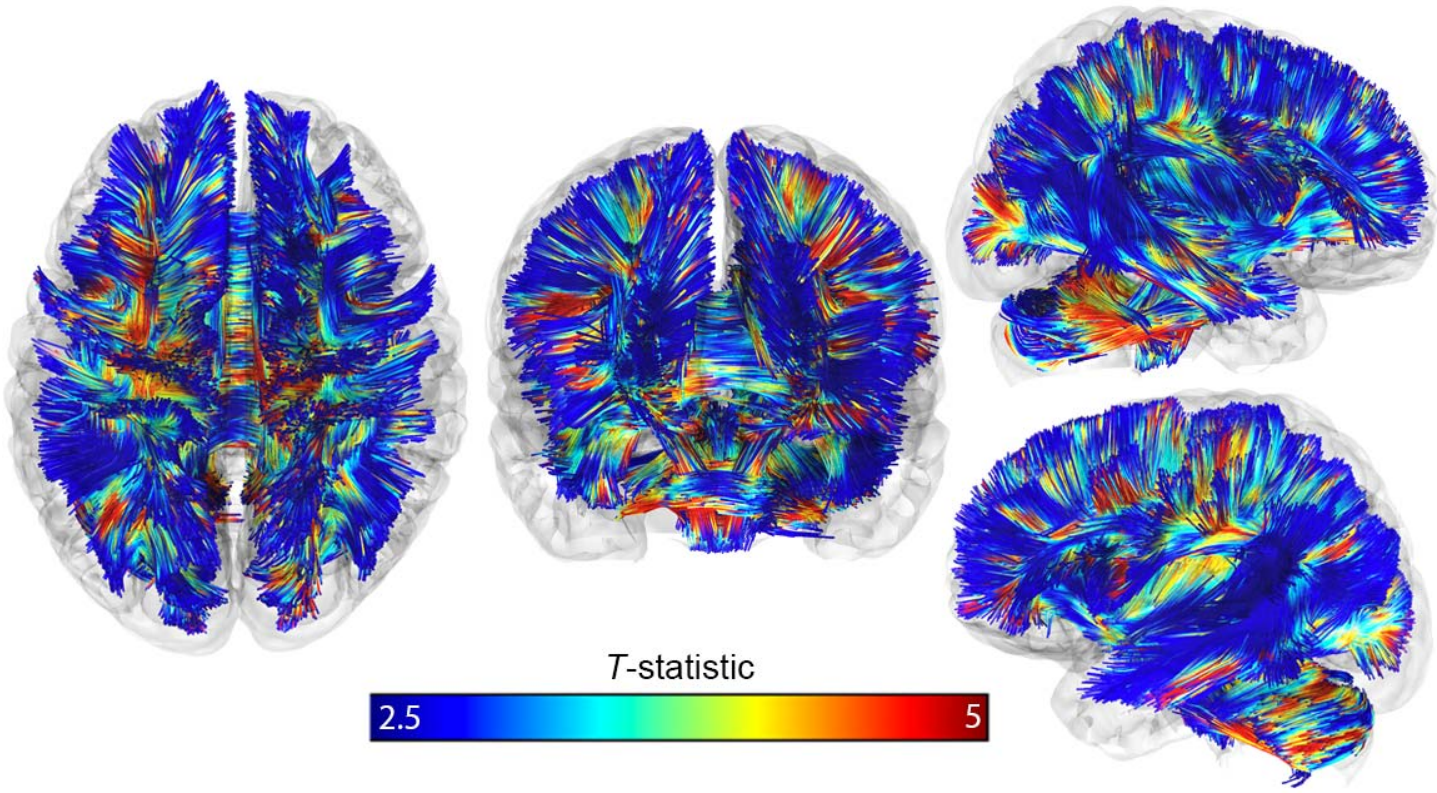

Figure 5. Differences in RDI in the post-acute and chronic phase. RDI was averaged across the regions showing significant differences between TBI-slow and TBI-normal at the chronic timepoint. RDI residuals are charted after accounting for age and sex. Red represents the control group, green represents the TBI-normal group, and blue represents the TBI-slow group. Cross-sectional differences are shown for the post-acute and chronic phases, with differences in longitudinal changes shown on the right. Statistically significant differences between groups (at $q<0.05$) are indicated within the graph with an asterisk.

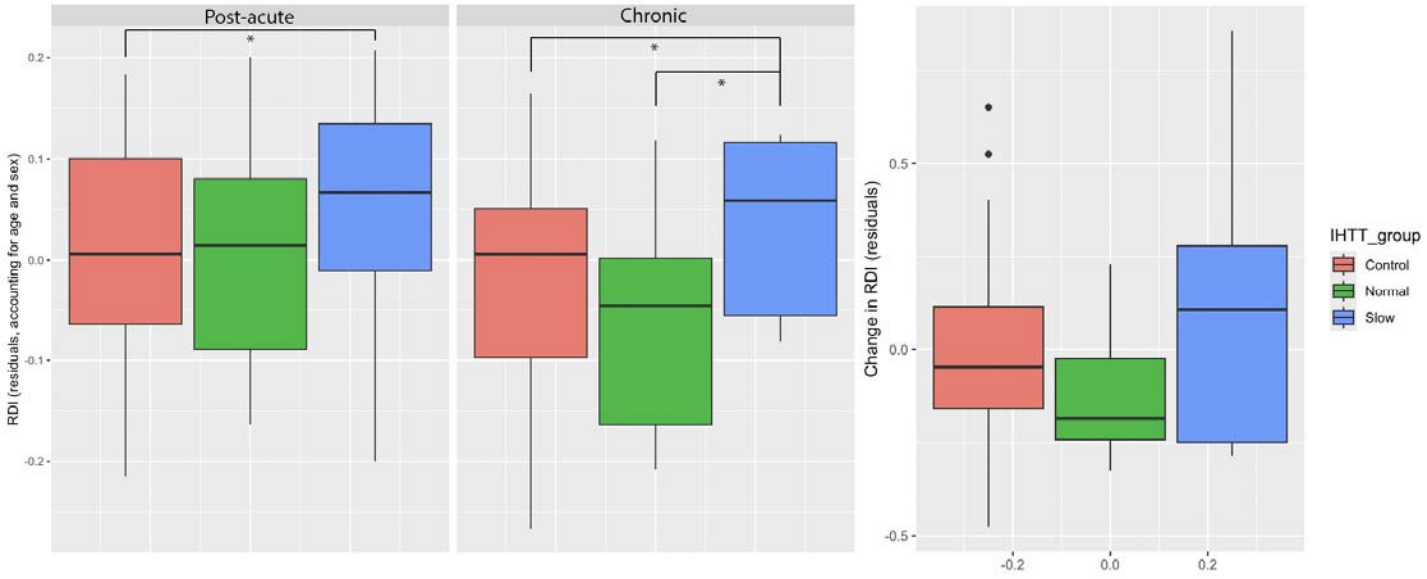

Figure 6. Associations between RDI and Cognitive Function. Along-tract negative associations between post-acute RDI and post-acute CPI in the TBI group. Colors correspond to *t*-statistics as shown in the color bar. Right in image is left in the brain. Right in image is right in the brain. Video: https://drive.google.com/drive/folders/191JGtHm5Oi5Lgnuix0ZqXHUyJ6VJ_roo