Abnormal neurite density and orientation dispersion in frontal lobe link to elevated hyperactive/impulsive behaviors in young adults with traumatic brain injury

Meng Cao¹#, Yuyang Luo¹#, Ziyan Wu²#, Kai Wu³, Xiaobo Li¹²*¹

¹ Department of Biomedical Engineering, New Jersey Institute of Technology, NJ, USA
² Department of Electrical and Computer Engineering, New Jersey Institute of Technology, NJ, USA
³ Department of Electrical and Computer Engineering, School of Materials Science and Engineering, South China University of Technology, Guangzhou, China

Running Title: Neurite morphometrical anomalies in TBI

# These authors contributed equally to the study

* Correspondence to:
Xiaobo Li, PhD
Associate Professor of Biomedical Engineering
New Jersey Institute of Technology
323 Martin Luther King Blvd, Fenster 613
Newark, NJ 07102, USA

Phone: 973-596-5880, Fax: 973-596-5222, Email: xli.aecom@gmail.com, xiaobo.li@njit.edu

© The Author(s) 2022. Published by Oxford University Press on behalf of the Guarantors of Brain. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.
Abstract

Traumatic brain injury is a major public health concern. A significant proportion of individuals experience post-traumatic brain injury behavioral impairments, especially in attention and inhibitory control domains. Traditional diffusion-weighted MRI techniques, such as diffusion tensor imaging, have provided tools to assess white matter structural disruptions reflecting the long-term brain tissue alterations associated with traumatic brain injury. The recently developed neurite orientation dispersion and density imaging is a more advanced diffusion MRI modality, which provides more refined characterization of brain tissue microstructures by assessing the neurite orientation dispersion and neurite density properties.

In this study, neurite orientation dispersion and density imaging data from 44 young adults with chronic traumatic brain injury (who had no prior-injury diagnoses of any sub-presentation of attention deficits/hyperactivity disorder or experience of severe inattentive and/or hyperactive behaviors) and 45 group-matched normal controls were investigated, to assess the post-injury morphometrical and microstructural brain alterations and their relationships with the behavioral outcomes. Maps of fractional anisotropy, neurite orientation dispersion index, and neurite density index were calculated. Vertex-wise and voxel-wise analyses were conducted for gray matter and white matter, respectively. Post-hoc region of interest-based analyses were also performed. Compared to the controls, the group of traumatic brain injury showed significantly increased orientation dispersion index and significantly decreased neurite density index in various gray matter regions, as well as significantly decreased orientation dispersion index in several white matter regions. Brain-behavioral association analyses indicated that the reduced neurite density index of left precentral gyrus and the reduced orientation dispersion index of left superior longitudinal fasciculus were significantly associated with elevated hyperactive/impulsive symptoms in the patients with traumatic brain injury. These findings suggest that post-injury chronical neurite intracellular volume and angular distribution anomalies in frontal lobe, practically the precentral area, can significantly contribute to the onset of hyperactive/impulsive behaviors in young adults with traumatic brain injury.
Keywords: Traumatic Brain Injury (TBI); Attention Deficits; Neurite Orientation Dispersion and Density Imaging (NODDI); Neurite Density Index (NDI); Orientation Dispersion Index (ODI).

Abbreviations: AD = axial diffusivity; ADHD = attention-deficit/hyperactivity disorder; ANCOVA = one-way analysis of covariates; CAARS = Conner’s Adult ADHD Self-Reporting Rating Scales; CSF = cerebrospinal fluid; dMRI = diffusion MRI; DTI = diffusion tensor imaging; FA = fractional anisotropy; fNIRS = functional near-infrared spectroscopy; FNIRT = FMRIB Nonlinear Registration Tool; FSL = FMRIB Software Library; FWE = family-wise error; GCS = Glasgow Coma Scale; GLM = general linear model; GM = gray matter; HCP = Human Connectome Project; IFOF = inferior fronto-occipital fasciculus; MD = mean diffusivity; MNI = Montreal Neurological Institute; MSM = multimodal surface matching; NC = normal control; NDI = neurite density index; NJIT = New Jersey Institute of Technology; NODDI = neurite orientation dispersion and density imaging; ODI = orientation dispersion index; RD = radial diffusivity; ROI = region of interest; RU = Rutgers University; SLF = superior longitudinal fasciculus; TBI = traumatic brain injury; TFCE = threshold-free cluster enhancement; WM = white matter.
Introduction

Traumatic brain injury (TBI) is a major public health concern, with about 2.8 million documented cases occurring each year in the United States, \(^1\) approximately 10 percent of which are due to sports and recreational activities. \(^2\) Although the acute symptoms of TBI may be transient and temperate, evidence is emerging that a significant proportion of patients experience long-lasting post-TBI cognitive, emotional, behavioral, sensory, and motoric changes. \(^3\) Among those post-TBI cognitive and behavioral disturbances, attention deficits are the most commonly reported, \(^4\) with the neuropathological natures remaining unclear.

The long-term post-TBI neural and psychophysiological anomalies have been suggested to relate to traumatic axonal injury that persists in a chronic stage. \(^5\) Loss of white matter (WM) integrity has been widely considered to play a major role in the clinical phenomenology of TBI. \(^6\) The pathology of diffuse axonal injury has been widely investigated in diffusion MRI (dMRI)-based approaches, especially diffusion tensor imaging (DTI) that is more sensitive than conventional T1- or T2-weighted imaging in detecting axonal injury. \(^7,8\) Among the DTI metrics, fractional anisotropy (FA) has been one of the most commonly reported measures in existing studies in TBI, with findings highly inconsistent in terms of involved brain regions as well as the trends (increase or reduction) of FA abnormalities. In particular, a number of existing studies indicated reduced FA in commonly affected WM tracts including corticospinal tract, \(^9\) sagittal stratum, \(^10\) and superior longitudinal fasciculus (SLF) \(^11\); corona radiata, \(^12\) uncinated fasciculus, \(^10,13\) corpus callosum, \(^12\) inferior longitudinal fasciculus, \(^13\) and cingulum bundle \(^13\); inferior fronto-occipital fasciculus (IFOF) \(^14\) among patients with chronic TBI relative to controls. While increased FA in corpus callosum, \(^15\) internal capsule, \(^16\) corticospinal tracts, \(^15\) corona radiate \(^16\) were also reported in subjects with a history of TBI as compared with matched controls. The discrepancy of these existing findings can be partially resulted from factors associated with the study samples, such as differences in injury severity and mechanism, time since the injury, cognitive and behavioral consequences, and sample sizes, as well as techniques implemented for data acquisition and analyses.
The FA value derived from DTI can be influenced by changes in axial diffusivity (AD), radial diffusivity (RD) within the brain tissues, or both, making FA sensitive to many types of brain pathology, while incapable for identifying the specific nature of the underlying pathology. In addition, although DTI can describe water diffusion behavior at modest b-values (e.g., 1000 s/mm$^2$), many studies have demonstrated that simple Gaussian diffusion models do not sufficiently describe water diffusion in complex tissues, such as crossing fibers and mixtures of diffusion compartments. Thus, conventional DTI approaches lack the ability to distinguish the spatial organization of neurites. Furthermore, multiple mechanisms, including changes in cell morphology and packing density, or changes in WM fiber orientation, would contribute to the alterations of FA. Recently, a more advanced dMRI modality, the neurite orientation dispersion and density imaging (NODDI), has been developed. This innovative technique acquires imaging data at multiple levels of diffusion weight, with each sampling many different spatial orientations at high angular resolution. The main parameters derived from NODDI are neurite density index (NDI), and neurite orientation dispersion index (ODI). The intracellular component of NODDI is designed to be representative of both axons and dendrites, thus providing an improved description of gray matter (GM) microstructure. In addition, NODDI enables differentiation of changes to tissue density and tissue ODI (both expressed by FA changes when using DTI), ultimately offering superior sensitivity to micro-level tissue changes. Recently, Churchill et al. conducted a NODDI study in adult athletes with and without TBI and reported significantly increased NDI and decreased ODI in corpus callosum and internal capsule in the TBI group. Besides, another recent study found that compared to conventional DTI, the NODDI parameters were more sensitive imaging biomarkers underlying WM microstructural pathology for relatively short-term (2 weeks and 6 months after TBI) consequences post mild TBI. Moreover, significant correlations between NODDI parameters and neurocognitive/behavioral outcomes have also been reported in patients with Alzheimer’s disease, autism spectrum disorders, and psychosis. However, the relationships between NODDI measures and TBI-related behaviors alterations have not been sufficiently investigated.
In this study, we proposed to utilize the refined measures provided by NODDI to investigate the neurobiological mechanisms that may underlie TBI-related attention deficits in young adults with chronic (> 6 months) TBI. Our previous functional near-infrared spectroscopy (fNIRS) studies that showed functional alterations in frontal areas during sustained attention processing in adults with TBI\textsuperscript{24,25}\textsuperscript{24,25}. In addition, our network studies also reported frontal and parietal abnormalities in both functional and structural brain networks in children with TBI.\textsuperscript{26,27}\textsuperscript{26,27} Based on the results of our previous studies, we hypothesized that neural morphometrical and microstructural abnormalities in frontal areas and the major WM fibers connecting frontal and other brain regions may exist, and significantly contribute to post-TBI attention-related behavioral alterations.

Materials and Methods

Participants

A total of 89 young adults (ranging from 18 - 26 years of age), including 44 patients with TBI (23 males/21 females) and 45 group-matched normal controls (NCs; 23 males /22 females), were initially involved in this study. Participants in the TBI group were recruited from sports teams at New Jersey Institute of Technology (NJIT) and Rutgers University (RU). The NCs were recruited through on-campus flyers at NJIT and RU. The study received Institutional Reviewed Board Approval at both NJIT and RU. Written informed consents were provided by all participants. Within these 89 subjects, 27 were involved in our previous fNIRS study.\textsuperscript{24}\textsuperscript{24}

The subjects with TBI had a history of one or multiple sports- or recreational activity-related non-penetrating TBIs, with the most recent onset of TBI clinically confirmed at least 6 months prior to the study visit; only had injuries rated as mild to moderate, characterized by the Glasgow Coma Scale (GCS)\textsuperscript{28}\textsuperscript{28}; had no head injury which ever caused overt focal brain damage; had no history of diagnosis with any sub-presentation of attention-deficit/hyperactivity disorder (ADHD) prior to the first onset TBI. The group of NCs included young adults with no history of head injury; had no history of diagnosis with...
ADHD; and had no severe inattentive and/or hyperactive/impulsive behaviors measured using the
Conner’s Adult ADHD Self-Reporting Rating Scales (CAARS, T-score < 60 for both inattention and
hyperactivity/impulsivity subscales) during the study visits. Subjects in both groups were native or fluent
speakers of English and strongly right-handed based on the Edinburgh Handedness Inventory. The study
excluded subjects who had a history or current diagnosis of any neurological disorders (such as epilepsy);
severe psychiatric disorders (including Schizophrenia, Autism Spectrum Disorders, Major Depression,
Anxiety, etc.); received treatment with any stimulant or non-stimulant psychotropic medication within the
month prior to testing; or had contraindications to MRI scanning. Demographic and clinical/behavioral
information of the study cohort was included in Table 1.

Four subjects were excluded from group-level analysis due to the heavy head motion (with either the
mean relative volume-to-volume displacement, maximum rotation, or maximum translation > 2.5mm).

Table 1: Demographic and clinical characteristics in groups of normal controls and traumatic brain
injury.

|                       | NC (N=40)       | TBI (N=43)       | p     |
|-----------------------|-----------------|-----------------|-------|
| Age (year)            | 21.40 (2.31)    | 21.02 (2.04)    | 0.432 |
| Education Level (year)| 14.70 (1.73)    | 14.23 (1.51)    | 0.192 |
| Mother’s Education Level (year) | 15.36 (2.21)    | 15.76 (2.62)    | 0.467 |
| Father’s Education Level (year) | 15.92 (2.99)    | 15.81 (2.36)    | 0.849 |
| Conners’ Adult ADHD Rating Scale (T score) |                 |                 |       |
| Inattentive           | 45.53 (6.43)    | 57.67 (15.28)   | <0.001|
| Hyperactive/Impulsive | 43.25 (5.65)    | 52.26 (13.72)   | <0.001|
| ADHD Total            | 44.03 (6.14)    | 56.67 (16.36)   | <0.001|
| Conners’ Adult ADHD Rating Scale (raw score) |                 |                 |       |
| Inattentive           | 4.50 (2.78)     | 9.53 (6.40)     | <0.001|
|                                | TBI: group of traumatic brain injury; NC: group of normal controls; SD: standard deviation |  |
|--------------------------------|----------------------------------------------------------------------------------------|--|---|
| Hyperactive/Impulsive          | 5.38 (2.59)                                                                             | 9.02 (5.39) | <0.001 |
| ADHD Total                     | 9.88 (4.69)                                                                             | 18.44 (10.65) | <0.001 |
|                                | N (%)         | N (%)          | p   |
| Male                           | 22 (55.0)    | 23 (53.5)     | 0.89 |
| Right-handed                   | 40 (100.0)   | 43 (100.0)    | 1.00 |
| Race                           |             |               | 0.127 |
| Caucasian                      | 13 (32.5)    | 22 (51.2)     |     |
| African American               | 3 (7.5)      | 7 (16.3)      |     |
| Hispanic/Latino                | 2 (5.0)      | 2 (4.7)       |     |
| Asian                          | 17 (42.5)    | 8 (18.6)      |     |
| More than one race             | 5 (12.5)     | 4 (9.3)       |     |

Neuroimaging Data Acquisition Protocol

High-resolution T1-weighted structural MRI (0.9 mm$^3$ isotropic T1w and T2w images) and dMRI data were acquired from a 3.0T Siemens Trio imaging system (Siemens, Erlangen, Germany). The three-dimensional dMRI images were acquired using a three-shell protocol with an echo planar imaging pulse sequence: TR/TE = 7700/103 ms, voxel size = 2.0 × 2.0 × 2.5 mm$^3$, number of slices = 55, FOV = 220 × 220 × 138 mm$^3$. The three shells of dMRI were consisted of 64 diffusion-weighting directions at b = 300 s/mm$^2$, 30 directions at b = 700 s/mm$^2$, and 10 directions at b = 2000 s/mm$^2$. In addition, six b0 scans with opposite phase encoding direction were collected for geometric distortion correction. The data of the b = 700 s/mm$^2$ shell were used for DTI analyses, while data from all three shells were used for NODDI analyses.
T1-weighted MRI data preprocessing were conducted using the Human Connectome Project (HCP) pipeline\(^{29}\) and FreeSurfer v6.0.\(^{10}\) After correction of gradient nonlinearity and field intensity, individual white and pial surfaces for surface-based analysis in GM were generated in the native spaces. Then each individual’s pial surface was non-linearly registered to the group-averaged pial surface using multimodal surface matching (MSM) algorithm.\(^{31}\)

The dMRI data preprocessing was performed using Diffusion Toolbox from FMRIB Software Library v6.0 (FSL; \texttt{www.fmrib.ox.ac.uk/fsl}).\(^{32}\) Before data preprocessing, the structural MRI and dMRI data from each subject were visually checked for severe head motions and heavy field distortions. Then, the susceptibility-induced field distortions, head motions, and eddy current distortion were corrected using \textit{topup} and \textit{eddy} from FSL. Four subjects with heavy head motions were excluded based on the motion parameters estimated by \textit{eddy}. The transformation matrices from local diffusion space to the structural space were calculated by registering a b0 volume to the T1-weighted image using FreeSurfer’s \textit{BBRegister}.\(^{33}\) Voxel-wise NODDI analyses were then conducted using the open-source MATLAB toolbox (\texttt{http://mig.cs.ucl.ac.uk/index.php?n=Tutorial.NODDImatlab}) with the “WatsonSHStickTortIsoV_B0” parameterization to distinguish three microstructural subcomponents: intracellular (neuritic), extracellular, and cerebrospinal fluid (CSF) compartments. The NODDI MATLAB toolbox was utilized to generate three parameter maps: 1) fraction of CSF (f\(_{\text{CSF}}\)), which indexes the volume fraction of Gaussian isotropic diffusion (free fluid) within each voxel; 2) NDI, which indicates the fraction of tissue water restricted within neuritis (axons and dendrites) in the non-CSF compartment. The intracellular signal was modelled as a Watson distribution over cylinders of zero radius, which has a mean orientation vector \(\mu\) and a concentration parameter \(\kappa \in (0, \infty)\) indicating how much the distribution tends to spread out around \(\mu\); and 3) ODI, transformed from the concentration parameter, which characterizes spatial configuration of neurites and ranges from 0 (completely parallel neurites) to 1 (completely random neurite orientation). In addition, the \(b = 700\) s/mm\(^2\) data series were...
analyzed to extract voxel-wise conventional DTI measure, FA, by using FSL’s *dtifit*. The individual-level data processing steps were shown in Fig. 1A.

**Surface-Based Analysis in GM**

The surface-based analysis in GM was conducted using the HCP’s connectome workbench and Freesurfer. First, the NDI and ODI maps of each individual were linearly transformed into native structural space. A ribbon mapping method, using WM surface as inner surface and pial surface as outer surface, was applied to sample the diffusion measures onto each individual’s surface at local space. This method was to construct a polyhedron for each vertex using the vertex’s neighbors, and to calculate the weight of each vertex based on the overlapping volumes with nearby voxels. To generate the vertex-based group difference map, the surface maps of NDI and ODI, were subsequently resampled onto the group-averaged surfaces (Fig. 1B) based on MSM surface registration.

**Tract-Based Spatial Statistics (TBSS) Analysis in WM**

TBSS of the NDI, ODI and FA maps were carried out in FSL (version 6.0.1). Firstly, FMRIB58_FA in the Montreal Neurological Institute (MNI) common space was used as the target image for nonlinear registration of all subjects’ FA maps, using the FMRIB Nonlinear Registration Tool (FNIRT; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FNIRT/). The transformed FA images in the MNI space were then averaged and skeletonized, to generate the major WM skeleton that would be implemented to all the subjects (Fig. 1C). The threshold of FA ≥ 0.2 was implemented to the average FA map to ensure the WM skeleton to include major WM tracts while exclude peripheral tracts and GM. Each participant’s aligned FA map was then projected onto this skeleton by assigning to each voxel the maximum FA in a line perpendicular to the local skeleton. The NDI, ODI, and isotropic compartment were projected onto the mean FA skeleton after applying the warping registration field of each subject to the standard MNI space.

**Statistical Analysis**
The group comparisons of the vertex-based measures in GM were performed using the Freesurfer’s
general linear model (GLM) analysis, with age, sex, and parent education level added as covariates. A
cluster-wise correction method, with a cluster of 25 mm² or greater and \( p < 0.05 \), were performed to
close for multiple comparisons. The anatomical regions with significant group differences on the GM
surface map were then identified using the Desikan-Killiany atlas.\(^{34}\)

Group comparisons of the voxel-based maps of NDI, ODI and FA in WM were performed in TBSS, using
the nonparametric statistical thresholding approach (FSL Randomise permutation algorithm;
https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise). The thresholded mean FA skeleton was used as a mask.
Two thousand permutations and statistical inference using threshold-free cluster enhancement (TFCE)
were performed, with \( p < 0.05 \) after family-wise error (FWE) correction for multiple comparisons. Age,
sex, and parent education level were used as covariates. The anatomic locations of regions with
significant group differences on the WM skeleton were identified from the Johns Hopkins University WM
labels atlas.

Based on the results from our previous studies\(^{24-27}\) and the result of vertex(voxel)-based analyses, a total
of 13 brain regions were selected for a further region of interest (ROI)-based analyses. The brain regions
consisted of 11 GM ROIs (right rostral middle frontal gyrus, right superior frontal gyrus, left superior
parietal lobule, bilateral caudal middle frontal gyrus, bilateral precentral gyrus, bilateral postcentral gyrus,
and bilateral paracentral lobules) and two WM ROIs (left IFOF and left SLF). The GM and WM ROIs
were defined based on the Desikan-Killiany atlas and the Johns Hopkins University WM probabilistic
tractography atlas, respectively. Mean ODI and NDI values within each ROI was extracted for each
subject (no between-group differences in FA were found during the voxel-based analyses). One-way
analysis of covariates (ANCOVA) was conducted to identify the between group differences, with age,
sex, and parent education level as covariates. Bonferroni correction was applied to control multiple
comparisons at significance level of 0.05.
Finally, ROI-based brain imaging measures that showed significant between-group differences were selected for correlation analysis with behavioral measures for clinical symptoms in inattentiveness and hyperactivity/impulsivity. Partial correlation between neuroimaging measures and T-scores of the CAARS inattentive and hyperactive/impulsive subscales were conducted in control and TBI group, respectively. Bonferroni correction was applied to control multiple comparisons at significance level of 0.05.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

Demographic, Clinical and Behavioral Measures

The demographic and clinical information of both TBI and NC groups were summarized in Table 1. Demographic measures did not show significant between-group difference. In the TBI group, 23 subjects had one injury, 12 subjects had two injuries, four subjects had three injuries, and four subjects had four injuries. Twenty-four subjects reported loss of consciousness for a short period. Seven subjects reported mild post-traumatic amnesia symptoms. The averaged time between the first injury and the scan was 5.6 (±3.6) years. Compared to the NCs, subjects with TBI showed significantly more clinical symptoms in inattentiveness and hyperactivity/impulsivity measured using the T- and raw-score of the CAARS inattentive and hyperactive/impulsive subscales. No significant correlations were found between the number of injuries and the CAARS inattentive ($r=0.021, p=0.892$) or hyperactive/impulsive ($r=0.085, p=0.589$) subscales.
Group Differences in the Intermediate Vertex (Voxel)-based Analyses

Group-level results of the surface-based analysis in GM showed significantly decreased NDI in vertex clusters from bilateral precentral gyrus, bilateral postcentral gyrus, left caudal middle frontal, right superior frontal gyrus, and right rostral middle frontal gyrus in patients, relative to controls (Fig. 2A). In addition, TBI group demonstrated significantly increased ODI in clusters of bilateral precentral gyrus, bilateral paracentral lobules, left precentral gyrus, left superior parietal lobule, and right middle frontal gyrus, when compared to NCs (Fig. 2B). All these regions showed $p < 0.05$ with a cluster greater than 25 mm².

Group-level results of TBSS in WM showed significantly decreased ODI in the left SLF ($p < 0.05$, TFCE corrected) and left IFOF ($p < 0.05$, TFCE corrected) in patients with TBI relative to NCs (Fig. 3A). No significant between-group differences were found in FA or NDI in WM.

Group Differences of ROI-based Imaging Measures

Compared to controls, the TBI group showed significantly abnormal neurite orientational integrity in bilateral frontal and parietal GM areas, represented by greatly increased ODI in bilateral middle frontal gyri, postcentral, precentral, and superior parietal gyri in the left hemisphere, as well as the superior frontal gyrus in the right hemisphere. Relative to controls, the adults with TBI also showed significantly decreased GM neurite density left precentral gyrus. The ROI-based analyses in WM showed significantly reduced ODI in left IFOF and SLF in the group of TBI. All the parameters of these results are detailed in Table 2 and graphically depicted in Fig. 2C and D and Fig. 3B, with all the $p$ values corrected using Bonferroni method. Additional ANCOVA was also performed by including race as an additional covariate, results were included in Supplementary Table 1. No significant effects of race were found on group differences.
Table 2: Anatomical regions that showed significant between-group differences of the neurite morphometry.

| Regions                        | Measures | NC (N=40) Mean (SD) | TBI (N=43) Mean (SD) | F    | p#  |
|-------------------------------|----------|---------------------|----------------------|------|-----|
| **Gray Matter ROIs**          |          |                     |                      |      |     |
| Left Caudal Middle Frontal    | ODI      | 0.537 (0.024)       | 0.556 (0.022)        | 18.17 | <0.001 |
| Left Postcentral Gyrus        | ODI      | 0.493 (0.035)       | 0.517 (0.027)        | 11.296 | 0.014 |
| Left Precentral               | ODI      | 0.509 (0.024)       | 0.529 (0.022)        | 19.743 | <0.001 |
|                              | NDI      | 0.568 (0.036)       | 0.545 (0.033)        | 9.903 | 0.026 |
| Left Superior Parietals       | ODI      | 0.503 (0.039)       | 0.535 (0.035)        | 12.813 | 0.007 |
| Right Caudal Middle Frontal   | ODI      | 0.542 (0.023)       | 0.559 (0.021)        | 15.024 | 0.003 |
| Right Superior Frontal        | ODI      | 0.529 (0.017)       | 0.542 (0.015)        | 16.512 | 0.001 |
| **White Matter ROIs**         |          |                     |                      |      |     |
| Left Inferior Fronto-occipital Fasciculus | ODI      | 0.266 (0.028)       | 0.251 (0.021)        | 8.115 | 0.012 |
| Left Superior Longitudinal Fasciculus | ODI    | 0.276 (0.022)       | 0.264 (0.022)        | 6.039 | 0.032 |

ROI: region-of-interest; TBI: group of traumatic brain injury; NC: group of normal controls; SD: standard deviation; ODI: orientation dispersion index; NDI: neurite density index; p#: p value after Bonferroni correction.

Brain-Behavior Correlations

In the group of TBI, reduced NDI of the left precentral gyrus and reduced ODI of the left SLF were both significantly correlated with elevated hyperactive/impulsive symptoms (Fig. 4). We did not find significant brain-behavior correlations in the group of NC. Detailed correlation analysis results were included in Supplementary Table 2 & 3. Brain-behavior correlations at voxel (voxel)-level were also available in Supplementary Figure 1 & 2.

Discussion

The present study investigated the neurite morphometry differences, represented by the NDI and ODI in both GM and WM areas, between young adults with TBI and group-matched controls. The results of
surface-based GM analysis reported significantly altered neurite morphometry in bilateral frontal and parietal areas, with the left frontal morphometrical abnormalities to be dominated in the subjects with TBI. In the literature of TBI-related studies, structural and functional abnormalities associated with frontal GM areas have been consistently reported in adults and children with TBI. For instance, relative to controls, TBI groups have been found to show significantly decreased frontal cortical thickness and significantly abnormal frontal neural activation during cognitive processing tasks. In addition, cortical GM thinning and functional alterations in parietal lobe have also been observed in both adults and children with TBI. Along with these existing findings, our results suggest that frontal and parietal GM regions are highly susceptible to the TBI-induced neurite intracellular volume and angular distribution anomalies that can be detected by the advanced NODDI technique, and these neuronal microstructural damages can contribute to the macro-level tissue morphometric and functional abnormalities in subjects with chronic TBI.

Our investigations in WM demonstrated that compared to the matched controls, subjects with TBI had significantly decreased ODI in the left SLF and left IFOF. The SLF and IFOF are two key components of the long-association fronto-parietal pathways, which interconnect cortical and subcortical areas to subserve the visuospatial attention and higher-order cognitive processes. Studies have suggested that SLF and IFOF are critical WM structures involving in the visuospatial orienting and executive components of attention processing, and brain regions associated with the orienting and executive components of visuospatial attention are most vulnerable to neural damages resulting from mild TBI. Indeed, substantial previous DTI studies in subjects with TBI have reported structural abnormalities of SLF and IFOF. For instance, significantly increased FA and decreased mean diffusivity (MD) in SLF and/or IFOF have been frequently reported in subjects with a history of sports-related concussion. While other studies in subjects with TBI have reported decreased FA and/or increased MD in left SLF and/or IFOF, and their linkages with prolonged post-TBI behavioral impairments. The inconsistence of these existing findings may be partially explained by the long-term effects of TBI appear to differ from
subacute concussion or chronicity of the injury, the severity level of TBI, and the limitation of DTI measures.

Furthermore, the results of the present study implicated that the significantly decreased NDI of left precentral gyrus and decreased ODI of the left SLF both significantly contribute to the elevated hyperactive/impulsive symptoms in individuals with TBI. These findings first time in the field suggest that both the TBI-related reduced GM neurite intracellular volume fraction in left frontal lobe and the overly aligned axons in left SLF that anatomically interconnecting frontal and parietal lobes can significantly contribute to TBI-related behavioral impairment in the domain of inhibitory control. The precentral gyrus has been consistently implicated in response inhibition in both primate and human studies. The SLF has also emerged as one of the most reliably identified WM tract underlying inhibitory, and variability in behavioral performances of inhibitory control-related tasks can be partially explained by variability in WM integrity of SLF. The reduced orientation dispersion in SLF reported in the current study might be caused by decreased branching of major bundles or degeneration of crossing fibers, which may potentially reduce the communication efficiency in attention related brain networks during inhibition process. Together with existing studies, our findings suggest that neurite density and orientation dispersion alterations in left frontal lobe, especially the precentral area, are significantly vulnerable in TBI-induced chronic neuronal damages; and these neuronal abnormalities significantly link to post-TBI behavioral impairments especially in the domain of inhibitory control.

Limitations

Although the current study utilized an innovative and robust dMRI technique to study the neurite morphometry and its relationship with post-TBI behavioral impairments in young adults with TBI and have reported significantly findings, we acknowledge that there are issues to be addressed. First, the sex factor associated with post-TBI attention deficits were not investigated due to the sample size limitation of the study. Existing studies indicated that, compared to males, females might have poorer
post TBI behavioral outcomes.\textsuperscript{62} However, our additional analyses in subgroups of females and males with TBI did not show significant differences in the clinical/behavioral and neuroimaging measures. To partially remove the potential effects, we added sex as a fixed effect covariate in the group-level analyses. A future study in a statistically powerful sample is expected to thoroughly investigate the sex-related post-TBI behavioral and anatomical alterations and their interactions. Second, we acknowledge that the diverse injury locations of TBI may be associated with different symptoms. Nevertheless, none of the existing studies have identified any patterns of association between a definitive injury location and long-term deficits in a specific domain of cognitive functions.

Conclusions

By utilizing an innovative dMRI technique, NODDI, the current study investigated the GM and WM neuronal morphometry and its relationship with post-TBI behavioral impairments in young adults with TBI. The results showed that relative to matched controls, the TBI subjects had significantly altered neurite density and orientation dispersion in frontal and parietal GM areas, and the WM tracts connecting these GM areas. We also found strong relationship of the abnormal left precentral GM NDI and SLF WM ODI with increased hyperactive/impulsive behaviors in the group of TBI. Our findings suggest that significantly altered neurite morphometry exists in frontal and parietal GM regions and the WM major tracts that anatomically connect these GM regions, especially in the left hemisphere; and these neurite disruptions significantly contribute to post-TBI attention problems in subjects with TBI. These findings provide valuable insight into the neuropathological markers of chronic TBI, which have the potential to inform biologically targeted prevention and intervention strategies in affected subjects.
Supplementary Material is available online at *Brain Communications*.

**Funding**

This study was partially supported by research grants from the National Institute of Mental Health (R03MH109791, R15MH117368, and R01MH060698) and the New Jersey Commission on Brain Injury Research (CBIR17PIL012).

**Competing Interests**

The authors report no competing interest.
References

1. Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic Brain Injury-Related Emergency Department Visits, Hospitalizations, and Deaths - United States, 2007 and 2013. *MMWR Surveill Summ.* Mar 17 2017;66(9):1-16. doi:10.15585/mmwr.ss6609a1

2. Centers for Disease C, Prevention. Nonfatal sports and recreation heat illness treated in hospital emergency departments--United States, 2001-2009. *MMWR Morb Mortal Wkly Rep.* Jul 29 2011;60(29):977-80.

3. De Beaumont L, Mongeon D, Tremblay S, et al. Persistent motor system abnormalities in formerly concussed athletes. *J Athl Train.* May-Jun 2011;46(3):234-40. doi:10.4085/1062-6050-46.3.234

4. Adeyemo BO, Biederman J, Zafonte R, et al. Mild traumatic brain injury and ADHD: a systematic review of the literature and meta-analysis. *J Atten Disord.* Oct 2014;18(7):576-84. doi:10.1177/1087054714543371

5. Rabinowitz AR, Levin HS. Cognitive sequelae of traumatic brain injury. *Psychiatr Clin North Am.* Mar 2014;37(1):1-11. doi:10.1016/j.psc.2013.11.004

6. Hughes DG, Jackson A, Mason DL, Berry E, Hollis S, Yates DW. Abnormalities on magnetic resonance imaging seen acutely following mild traumatic brain injury: correlation with neuropsychological tests and delayed recovery. *Neuroradiology.* Jul 2004;46(7):550-8. doi:10.1007/s00234-004-1227-x

7. Hulkower MB, Poliak DB, Rosenbaum SB, Zimmerman ME, Lipton ML. A decade of DTI in traumatic brain injury: 10 years and 100 articles later. *AJNR Am J Neuroradiol.* Nov-Dec 2013;34(11):2064-74. doi:10.3174/ajnr.A3395

8. Mac Donald CL, Dikranian K, Bayly P, Holtzman D, Brody D. Diffusion tensor imaging reliably detects experimental traumatic axonal injury and indicates approximate time of injury. *J Neurosci.* Oct 31 2007;27(44):11869-76. doi:10.1523/JNEUROSCI.3647-07.2007

9. Kraus MF, Susmaras T, Caughlin BP, Walker CJ, Sweeney JA, Little DM. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain.* Oct 2007;130(Pt 10):2508-19. doi:10.1093/brain/awm216

10. Geary EK, Kraus MF, Pliskin NH, Little DM. Verbal learning differences in chronic mild traumatic brain injury. *J Int Neuropsychol Soc.* May 2010;16(3):506-16. doi:10.1017/S135561771000010X

11. Matthews SC, Strigo IA, Simmons AN, O’Connell RM, Reinhardt LE, Moseley SA. A multimodal imaging study in U.S. veterans of Operations Iraqi and Enduring Freedom with and without major depression after blast-related concussion. *Neuroimage.* Jan 2011;54 Suppl 1:S69-75. doi:10.1016/j.neuroimage.2010.04.269

12. Churchill NW, Caverzasi E, Graham SJ, Hutchison MG, Schweizer TA. White matter during concussion recovery: Comparing diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI). *Hum Brain Mapp.* Apr 15 2019;40(6):1908-1918. doi:10.1002/hbm.24500

13. Niogi SN, Mukherjee P, Ghajar J, et al. Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: a 3T diffusion tensor imaging study of mild traumatic brain injury. *AJNR Am J Neuroradiol.* May 2008;29(5):967-73. doi:10.3174/ajnr.A0970
14. Singh M, Jeong J, Hwang D, Sungkarat W, Gruen P. Novel diffusion tensor imaging methodology to detect and quantify injured regions and affected brain pathways in traumatic brain injury. *Magn Reson Imaging*. Jan 2010;28(1):22-40. doi:10.1016/j.mri.2009.05.049

15. Henry LC, Tremblay J, Tremblay S, et al. Acute and chronic changes in diffusivity measures after sports concussion. *J Neurotrauma*. Oct 2011;28(10):2049-59. doi:10.1089/neu.2011.1836

16. Sasaki T, Pasternak O, Mayinger M, et al. Hockey Concussion Education Project, Part 3: White matter microstructure in ice hockey players with a history of concussion: a diffusion tensor imaging study. *J Neurosurg*. Apr 2014;120(4):882-90. doi:10.3171/2013.12.JNS132092

17. Pierpaoli C, Basser PJ. Toward a quantitative assessment of diffusion anisotropy. *Magn Reson Med*. Dec 1996;36(6):893-906. doi:10.1002/mrm.1910360612

18. Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. *Neuroimage*. Jul 16 2012;61(4):1000-16. doi:10.1016/j.neuroimage.2012.03.072

19. Churchill NW, Caverzasi E, Graham SJ, Hutchison MG, Schweizer TA. White matter microstructure in athletes with a history of concussion: Comparing diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI). *Hum Brain Mapp*. Aug 2017;38(8):4201-4211. doi:10.1002/hbm.23658

20. Palacios EM, Owen JP, Yuh EL, et al. The evolution of white matter microstructural changes after mild traumatic brain injury: A longitudinal DTI and NODDI study. *Sci Adv*. Aug 2020;6(32):eaaz6892. doi:10.1126/sciadv.aaz6892

21. Parker TD, Slattery CF, Zhang J, et al. Cortical microstructure in young onset Alzheimer's disease using neurite orientation dispersion and density imaging. *Hum Brain Mapp*. Jul 2018;39(7):3005-3017. doi:10.1002/hbm.24056

22. Andica C, Kamagata K, Kirino E, et al. Neurite orientation dispersion and density imaging reveals white matter microstructural alterations in adults with autism. *Mol Autism*. Jun 30 2021;12(1):48. doi:10.1186/s13229-021-00456-4

23. Kraguljac NV, Monroe WS, Anthony T, Jindal RD, Hill H, Lahti AC. Neurite Orientation Dispersion and Density Imaging (NODDI) and duration of untreated psychosis in antipsychotic medication-naive first episode psychosis patients. *Neuroimage: Reports*. 2021/03/01/ 2021;1(1):100005. doi:https://doi.org/10.1016/j.jynirp.2021.100005

24. Wu Z, Mazzola CA, Catania L, et al. Altered cortical activation and connectivity patterns for visual attention processing in young adults post-traumatic brain injury: A functional near infrared spectroscopy study. *CNS Neurosci Ther*. Jun 2018;24(6):539-548. doi:10.1111/cns.12811

25. Koenig S, Wu Z, Gao Y, Li X. Abnormal Cortical Activation in Visual Attention Processing in Sub-Clinical Psychopathic Traits and Traumatic Brain Injury: Evidence from an fNIRS Study. *Journal of Psychopathology and Behavioral Assessment*. 2020/12/01 2020;42(4):627-636. doi:10.1007/s10862-020-09808-5

26. Cao M, Halperin JM, Li X. Abnormal Functional Network Topology and Its Dynamics during Sustained Attention Processing Significantly Implicate Post-TBI Attention Deficits in Children. *Brain Sci*. Oct 13 2021;11(10) doi:10.3390/brainsci11101348

27. Cao M, Luo Y, Wu Z, et al. Topological Aberrance of Structural Brain Network Provides Quantitative Substrates of Post-Traumatic Brain Injury Attention Deficits in Children. *Brain Connect*. May 6 2021;doi:10.1089/brain.2020.0866
28. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. Jul 13 1974;2(7872):81-4. doi:10.1016/s0140-6736(74)91639-0

29. Glasser MF, Sotiropoulos SN, Wilson JA, et al. The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage*. Oct 15 2013;80:105-24. doi:10.1016/j.neuroimage.2013.04.127

30. Fischl B. FreeSurfer. *Neuroimage*. 2012;62(2):774-781.

31. Robinson EC, Jbabdi S, Glasser MF, et al. MSM: a new flexible framework for Multimodal Surface Matching. *Neuroimage*. Oct 15 2014;100:414-26. doi:10.1016/j.neuroimage.2014.05.069

32. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*. 2004;23 Suppl 1:S208-19.

33. Greve DN, Fischl B. Accurate and robust brain image alignment using boundary-based registration. *Neuroimage*. Oct 15 2009;48(1):63-72. doi:10.1016/j.neuroimage.2009.06.060

34. Desikan RS, Segonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. Jul 1 2006;31(3):968-80. doi:10.1016/j.neuroimage.2006.01.021

35. Mayer AR, Hanlon FM, Ling JM. Gray matter abnormalities in pediatric mild traumatic brain injury. *J Neurotrauma*. May 15 2015;32(10):723-30. doi:10.1089/neu.2014.3534

36. Turken AU, Herron TJ, Kang X, et al. Multimodal surface-based morphometry reveals diffuse cortical atrophy in traumatic brain injury. *BMC Med Imaging*. Dec 31 2009;9:20. doi:10.1186/1471-2342-9-20

37. Wilde EA, Newsome MR, Bigler ED, et al. Brain imaging correlates of verbal working memory in children following traumatic brain injury. *Int J Psychophysiol*. Oct 2011;82(1):86-96. doi:10.1016/j.ijpsycho.2011.04.006

38. McAllister TW, Sparling MB, Flashman LA, Guerin SJ, Mamourian AC, Saykin AJ. Differential working memory load effects after mild traumatic brain injury. *Neuroimage*. Nov 2001;14(5):1004-12. doi:10.1006/nimg.2001.0899

39. Keightley ML, Saluja RS, Chen JK, et al. A functional magnetic resonance imaging study of working memory in youth after sports-related concussion: is it still working? *J Neurotrauma*. Mar 1 2014;31(5):437-51. doi:10.1089/neu.2013.3052

40. Govindarajan KA, Narayana PA, Hasan KM, et al. Cortical Thickness in Mild Traumatic Brain Injury. *J Neurotrauma*. Oct 15 2016;33(20):1809-1817. doi:10.1089/neu.2015.4253

41. Urban KJ, Riggs L, Wells GD, et al. Cortical Thickness Changes and Their Relationship to Dual-Task Performance following Mild Traumatic Brain Injury in Youth. *J Neurotrauma*. Feb 15 2017;34(4):816-823. doi:10.1089/neu.2016.4502

42. Dettwiler A, Murugavel M, Putukian M, Cubon V, Furtado J, Osherson D. Persistent differences in patterns of brain activation after sports-related concussion: a longitudinal functional magnetic resonance imaging study. *J Neurotrauma*. Jan 15 2014;31(2):180-8. doi:10.1089/neu.2013.2983

43. Thiebaut de Schotten M, Dell’Acqua F, Forkel SJ, et al. A lateralized brain network for visuospatial attention. *Nat Neurosci*. Sep 18 2011;14(10):1245-6. doi:10.1038/nn.2905

44. Chechlacz M, Gillebert CR, Vangkilde SA, Petersen A, Humphreys GW. Structural Variability within Frontoparietal Networks and Individual Differences in Attentional Functions: An Approach Using the Theory of Visual Attention. *J Neurosci*. Jul 29 2015;35(30):10647-58. doi:10.1523/JNEUROSCI.0210-15.2015
45. Fan J, McCandliss BD, Sommer T, Raz A, Posner MI. Testing the efficiency and independence of attentional networks. J Cogn Neurosci. Apr 1 2002;14(3):340-7. doi:10.1162/089892902317361886
46. Halterman CI, Langan J, Drew A, et al. Tracking the recovery of visuospatial attention deficits in mild traumatic brain injury. Brain. Mar 2006;129(Pt 3):747-53. doi:10.1093/brain/awh705
47. Bendlin BB, Ries ML, Lazar M, et al. Longitudinal changes in patients with traumatic brain injury assessed with diffusion-tensor and volumetric imaging. Neuroimage. Aug 15 2008;42(2):503-14. doi:10.1016/j.neuroimage.2008.04.254
48. Cubon VA, Putukian M, Boyer C, Dettwiler A. A diffusion tensor imaging study on the white matter skeleton in individuals with sports-related concussion. J Neurotrauma. Feb 2011;28(2):189-201. doi:10.1089/neu.2010.1430
49. Murugavel M, Cubon V, Putukian M, et al. A longitudinal diffusion tensor imaging study assessing white matter fiber tracts after sports-related concussion. J Neurotrauma. Nov 15 2014;31(22):1860-71. doi:10.1089/neu.2014.3368
50. Ling JM, Pena A, Yeo RA, et al. Biomarkers of increased diffusion anisotropy in semi-acute mild traumatic brain injury: a longitudinal perspective. Brain. Apr 2012;135(Pt 4):1281-92. doi:10.1093/brain/aws073
51. Wilde EA, McCauley SR, Hunter JV, et al. Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. Neurology. Mar 18 2008;70(12):948-55. doi:10.1212/01.wnl.0000305961.68029.54
52. Wu YC, Mustafi SM, Harezlak J, Kodiveera C, Flashman LA, McAllister TW. Hybrid Diffusion Imaging in Mild Traumatic Brain Injury. J Neurotrauma. Oct 15 2018;35(20):2377-2390. doi:10.1089/neu.2017.5566
53. Li CS, Huang C, Constable RT, Sinha R. Imaging response inhibition in a stop-signal task: neural correlates independent of signal monitoring and post-response processing. J Neurosci. Jan 4 2006;26(1):186-92. doi:10.1523/JNEUROSCI.3741-05.2006
54. Swann N, Tandon N, Canolty R, et al. Intracranial EEG reveals a time- and frequency-specific role for the right inferior frontal gyrus and primary motor cortex in stopping initiated responses. J Neurosci. Oct 7 2009;29(40):12675-85. doi:10.1523/JNEUROSCI.3359-09.2009
55. Picazio S, Veniero D, Ponzo V, et al. Prefrontal control over motor cortex cycles at beta frequency during movement inhibition. Curr Biol. Dec 15 2014;24(24):2940-5. doi:10.1016/j.cub.2014.10.043
56. Narayanan NS, Laubach M. Top-down control of motor cortex ensembles by dorsomedial prefrontal cortex. Neuron. Dec 7 2006;52(5):921-31. doi:10.1016/j.neuron.2006.10.021
57. Cristofori I, Zhong W, Chau A, Solomon J, Krueger F, Grafman J. White and gray matter contributions to executive function recovery after traumatic brain injury. Neurology. Apr 7 2015;84(14):1394-401. doi:10.1212/01.wnl.0000000000001446
58. Karlsrud KH, Bato AA, Blair MA, DeRosse P, Szaszko PR, Malhotra AK. White matter microstructure in the executive network associated with aggression in healthy adolescents and young adults. Soc Cogn Affect Neurosci. Sep 2015;10(9):1251-6. doi:10.1093/scan/nsv015
59. Mabott DJ, Noseworthy M, Bouffet E, Laughlin S, Rockel C. White matter growth as a mechanism of cognitive development in children. Neuroimage. Nov 15 2006;33(3):936-46. doi:10.1016/j.neuroimage.2006.07.024
60. Urger SE, De Bellis MD, Hooper SR, Woolley DP, Chen SD, Provenzale J. The superior longitudinal fasciculus in typically developing children and adolescents: diffusion tensor imaging and neuropsychological correlates. *J Child Neurol*. Jan 2015;30(1):9-20. doi:10.1177/0883073813520503

61. Li P, Tsapanou A, Qolamreza RR, Gazes Y. White matter integrity mediates decline in age-related inhibitory control. *Behav Brain Res*. Feb 26 2018;339:249-254. doi:10.1016/j.bbr.2017.11.005

62. Broshek DK, Kaushik T, Freeman JR, Erlanger D, Webbe F, Barth JT. Sex differences in outcome following sports-related concussion. *J Neurosurg*. May 2005;102(5):856-63. doi:10.3171/jns.2005.102.5.0856
Figure Legends

Figure 1. Overview of the study methods. (A) Individual-level data preprocessing. (B) Surface-based analysis of GM. (C) Voxel-based analysis of WM. (D) Group-level statistical analysis. NC: normal controls; TBI: traumatic brain injury; NODDI: neurite orientation dispersion and density imaging; GM: gray matter; WM: white matter; TBSS: tract-based spatial statistics; CAARS: Conner’s adult attention-deficit/hyperactivity disorder self-reporting rating scales; ROI: region of interest.

Figure 2. Surface-based analysis of neurite properties in gray matter. (A) Surface-based gray matter analysis showing clusters that have significantly higher NDI in NC than TBI. (B) Surface-based gray matter analysis showing clusters that have significantly lower ODI in NC than TBI. (C) Region-of-interest-based group comparison in NDI. TBI group showed significantly decreased NDI in L.PreCG (F=9.903, p=0.026) when compared with controls. (D) Region-of-interest-based group comparison in ODI. TBI group showed significantly increased ODI in L.cMFG (F=18.17, p<0.001), L.PreCG (F=19.743, p<0.001), L.PostCG (F=11.296, p=0.014), L.SPG (F=12.813, p=0.007), R.cMFG (F=15.023, p=0.003), and R.SFG (F=16.512, p=0.001) when compared with controls. Regions that showed significant group difference (one-way analysis of covariates; p<0.05 after Bonferroni correction) were marked with asterisk (*). The bars indicate the maximum and minimum values, the solid horizontal lines in the middle represent the median, and the boxes represent the inner quartile range. NDI: neurite density index; ODI: orientation dispersion index; TBI: traumatic brain injury; NC: normal controls; L: Left; R: Right; cMFG: caudal middle frontal gyrus; PreCG: precentral gyrus; ParaCG: paracentral gyrus; PostCG: postcentral gyrus; SPG: superior parietal gyrus; rMFG: rostral middle frontal gyrus; SFG: superior frontal gyrus.

Figure 3. Voxel-level and region-of-interest analysis of white matter. (A) Tract-based spatial statistics results showing significant between-group differences of voxel-wise ODI for groups of TBI and normal controls. (B) Region of interest analysis results showed significant between group differences (one-way
analysis of covariates, $p<0.05$ after Bonferroni correction) in the groups of NC and TBI. TBI group showed significantly decreased ODI in left superior longitudinal fasciculus ($F=6.039$, $p=0.032$) and left inferior fronto-occipital fasciculus ($F=8.115$, $p=0.012$) when compared with controls. Top panel presents the results in left superior longitudinal fasciculus; bottom panel presents the results in left inferior fronto-occipital fasciculus. The bars indicate the maximum and minimum values, the solid horizontal line in the middle represent the median, and the boxes represent the inner quartile range. TBI: traumatic brain injury; NC: normal controls; ODI: orientation dispersion index.

**Figure 4. Brain-behavior correlation analysis results.** (A) Increased neurite density index of left precentral gyrus was significantly correlated with reduced hyperactive/impulsive symptom severity T-score in the group TBI. (B) Greater orientation dispersion index of left superior longitudinal fasciculus was significantly correlated with reduced hyperactive/impulsive symptom severity T-score in the group TBI. TBI: traumatic brain injury.
Figure 1
144x135 mm (4.0 x DPI)
Figure 2

165x118 mm (4.0 x DPI)
Figure 3
165x72 mm (4.0 x DPI)
Figure 4

Panel A: Left Precentral Gyrus

- Neurite Density Index vs. T score for Hyperactive/Impulsive Symptom
- $r = -0.406$
- $p = 0.014$

Panel B: Left Superior Longitudinal Fasciculus

- Orientation Dispersion Index vs. T score for Hyperactive/Impulsive Symptom
- $r = -0.324$
- $p = 0.043$