Neurology Asia 2024; 29(4) : 1141 – 1154

A novel application of neurite orientation dispersion and density imaging to differentiate cognitively recovered versus non-recovered following mild traumatic brain injury

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Abstract

Objective: Cognitive deficits in mild traumatic brain injury (mTBI) can persist over three months, and symptomatic patients may not be readily diagnosed. Although diffusion tensor imaging (DTI) can detect microstructural white matter tract (WMT) changes in mTBI, the underlying recovery process is not fully understood. We aimed to investigate WMT changes at 3 months post-mTBI between cognitively recovered (REC) and non-recovered (NREC) mTBI subjects using diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI). *Methods:* Fifty-seven mTBI subjects were divided into REC (n=16) and NREC (n=41) groups. Ten healthy controls (HC) were recruited. MRI and Neuropsychological Assessment Battery-Screening Module (S-NAB) performance were assessed at baseline and three months before subjects were classified as REC and NREC. DTI and NODDI parameters of 50 ROIs corresponding to WMTs were compared between REC, NREC and HC. *Results:* NODDI detected more significant changes ($p<0.05$) in multiple ROIs than DTI. Lower Neurite Density Index (NDI) was demonstrated in REC versus NREC at multiple ROIs. Increased Orientation Dispersion Index (ODI) and decreased Isotropic Volume Fraction (ISOVF) were detected at several WMTs in both groups.
Conclusion: Reduced NDI in the overall mTBI cohort suggests axonal degeneration post-trauma. We postulate that at three months' timeline, there is a combination of axonal degeneration and astrogliosis, which is more extensive in NREC than REC.

Keywords: Mild traumatic brain injury, NODDI, DTI, cognitive impairment

INTRODUCTION

Mild traumatic brain injury (mTBI) occurs due to blunt injury to the head, leading to physiological disruption of brain function. Road traffic accidents are the commonest cause of TBI worldwide.[1] Road traffic accidents (RTA) are the second largest cause of mTBI, after falls.[2] Cognitive symptoms are detectable from 48 hours to two weeks after injury[3,4], with good recovery in most mTBI patients within the first three months.[3,5] Cognitive rehabilitation is recommended if cognitive impairment persists.[6,7]

Diagnosis of mTBI is primarily clinical.[8,9] Pathophysiological evidence, has reported mTBI to be a diffuse, microscopic (axonal) phenomenon10 which may not be detectable on computed tomography (CT) or conventional magnetic resonance imaging (MRI) sequences.[11,12] Diffusion tensor imaging (DTI), with its unicompartmental water diffusion model, has been used to detect microstructural changes in TBI.[13,14]

Heterogeneous outcomes of DTI studies on mTBI[14,15] further question DTI sensitivity in detecting, and specificity in explaining the pathophysiology behind these changes in traumatic axonal injury (TAI)[15,16], spurring the

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Date of Submission: 24 June 2024; Date of Acceptance: 31 August 2024
https://doi.org/10.54029/2024exe

search for new imaging methods with improved detection accuracy across various injury stages.[16,17]

Neurite Orientation Dispersion And Density Imaging (NODDI) utilises the fraction of water molecules in three different compartments: intracellular, extracellular (space immediately around a neurite), and free water (CSF) compartments, thereby improving the sensitivity and specificity of detection of TAI and WM microstructural changes.[16,18] The intracellular volume fraction gives the Neurite Density Index (NDI), analogous to neurites' density in a voxel.[16] Orientation Dispersion Index (ODI) measures how dispersed the neurites are in a voxel.[16] The isotropic volume fraction (ISOVF) gives the free water content in a voxel.[4,16] ISOVF represents the CSF; however, an increase may indicate vasogenic oedema.[4,16]

A NODDI and DTI study at 6 to 12 months post-mTBI revealed reduced FA and increased ODI, which was attributed to reduced axonal bundle coherence.[15] A study on athletes at over 6 months post-sport concussion showed elevated FA, increased NDI and decreased ODI, with greater effects among athletes who were imaged a longer time since their last concussion.[19] A longitudinal study on concussed athletes in the acute and subacute phase of mTBI showed that those with worse symptoms had lower FA and increased ODI.[20]

In this study, we aimed to perform an exploratory analysis to i) investigate white matter microstructural changes after mTBI at 3 months post-trauma between cognitively recovered and non-recovered mTBI patients, and ii) compare the use of DTI and NODDI in determining white matter tract (WMT) changes in mTBI.

Only subjects with an impaired baseline neuropsychological assessment were included in this study to enable us to associate the baseline cognitive impairment with the occurrence of mTBI. The inclusion criteria are to demonstrate that the non-recovered group had persistent cognitive impairment from the subacute (two-week to three months) to chronic mTBI (three months and beyond).[21-23] In contrast, the recovered group had improved (normalized) cognition.

METHODS

Study design and participants

This was a cross-sectional single-centre study approved by the local Medical Research Ethics Committee. All patients who were clinically diagnosed with mTBI in the Emergency and Trauma Department of a Level III Trauma centre from August 2017 to August 2019 were recruited.

Mild TBI is defined as a physiological disruption of brain function due to trauma with a loss of consciousness of 30 minutes or less, a focal neurological deficit that may or may not be transient, an altered mental state with a Glasgow Coma Scale of 13-15 and loss of memory with post-traumatic amnesia not greater than 24 hours.[8] All participants had undergone plain brain CT on admission. 57 subjects with reported normal CT brain findings and fulfilling inclusion criteria were considered for recruitment (Figure 1).

Inclusion criteria

Adult patients between the age of 18 to 60 years; with mTBI due to road traffic accidents (RTA); no previous history of head trauma, able to give informed consent, and abnormal Neuropsychological assessment Battery – Screening Module (S-NAB) result (<85) at two weeks assessment.

Exclusion criteria

Subjects with a normal baseline S-NAB score, pre-existing chronic illness that caused neurological symptoms or complications; pre-existing neurological or psychiatric disorder; prescribed medication that affected cognitive and psychological status; evidence of substance intoxication at the time of injury; major polytrauma, abnormal findings on admission CT brain and absolute contraindication for MRI.

Healthy control group (HC)

Ten healthy individuals were demographically matched for age and education years to the mTBI group. They consisted of adults between 18 and 60 with no history of previous head trauma, chronic neurological or psychiatric condition. They were matched demographically and in years of schooling with the mTBI groups. They also underwent both S-NAB and MRI for comparison purposes.

Outcome measures

Neuropsychological assessment

S-NAB consists of 12 individual tests, screening all five cognitive domains for adults aged 18 to 97 years, validated and sensitive for healthy and cognitively impaired brain-injured populations.[24]

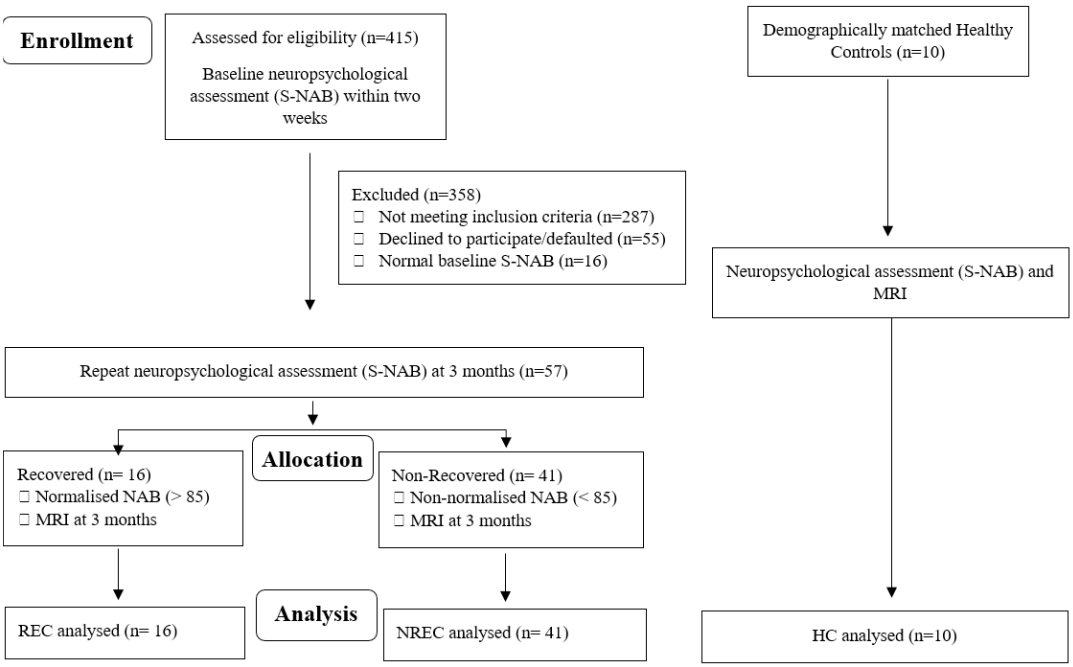

Figure 1. Recruitment diagram and time frame for MRI examination and assessment.

S-NAB also provides two parallel assessment sets applied in an alternate fashion to avoid practice effects. Each screening domain score is scaled to have a mean of 100 (SD = 15). A screening domain score of less than 85 is categorized to be in the impaired range, and a score greater than 85 is in the non-impaired range as set by the S-NAB manual.[6] A lower score value implies poorer cognitive performance.

Upon enrolment of the study a baseline neuropsychological assessment (S-NAB) was done by a neuro-rehabilitation doctor (NH) within 2 weeks of trauma. A repeat S-NAB assessment was done at 3 months. mTBI subjects were then divided into two groups (i) recovered group (REC) with normalized S-NAB score (average score above 85) and (ii) non-recovered group (NREC) with non-normalized S-NAB score (average score below 85) (Figure 1).

Upon recruitment of healthy control (HC) participants, a neurocognitive assessment (S-NAB) was performed.

Magnetic resonance imaging

MRI was performed using a 3.0 Tesla Siemens MAGNETOM Prisma® scanner (Siemens Healthcare) equipped with a dedicated 20-channel head coil at three months post-trauma after completing S-NAB assessment for mTBI (REC and NREC groups). For HC, MRI was performed within a week after the baseline S-NAB test.

Whole-brain NODDI was performed using a monoplanar pulse sequence (echo time [TE] = 122ms; repetition time [TR] = 4900ms) using 30 diffusion encoding directions at b = 0s/mm2, b = 700s/mm2 and b = 2800s/mm2, slice thickness of 3mm with no interslice gap, an 80 x 80 matrix and a field of view (FOV) of 240 x 240mm [Acquisition time of 5min 25sec]. Raw data for DTI was obtained from the b = 700s/mm2 shell. Axial T1-weighted (T1 mprage) (TE = 2.43ms, TR = 2200ms, a 224 x 224 matrix, FOV of 230 x 230mm, slice thickness of 1mm) [Acquisition time of 4min 59sec].

DTI

DTI analysis was done using the Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library (FSL).25 Images were first corrected for motion and distortion using b = 0 s/mm2 data volumes for each shell as reference. Fractional anisotropy (FA) and mean diffusivity (MD) maps were calculated using the FSL Diffusion Toolbox.

NODDI

NODDI metrics were derived from the raw images using the Accelerated Microstructure Imaging via Convex Optimization software (AMICO)[26] for diffusion MRI data. Maps of ODI, NDI, and

ISOVF were generated. Skeleton maps were obtained using the FSL Diffusion Toolbox, as in the DTI methodology.

Region of interest (ROI)-based analysis

Tract-Based Spatial Statistics (TBSS)[27], part of FMRIB Software Library (FSL), was used to register and normalize the image data to standard space. FA data was registered onto the FMRIB58 FA template using a non-linear algorithm in the MNI152 standard space. A mean FA white matter skeleton was then created from the images of all tracts of every subject in a group. The DTI (FA, MD) and NODDI (ODI, NDI, ISOVF) parameters of all subjects were then projected onto the skeleton using the derived projection vectors from the mean FA white matter skeleton.

Fifty regions of interest (ROIs) designated T1 to T50 corresponding to 50 WMTs were studied using masks obtained from the ICBM-DTI-81 White Matter Labels Atlas (ICBM DTI Workgroup).[28,29] Mask images from the studied WMTs were used to mask individual skeletonized maps previously registered to the MNI152 standard space. Mean ODI, NDI, ISOVF, FA, and MD values were obtained for each ROI from each subject's white matter skeletonised tract.

Statistical analysis

SPSS version 25.0(30) was used for data analysis. Tests of normality (Kolmogorov-Smirnov) showed that 96% of DTI and NODDI metrics at each ROI were normally distributed. Data analysis of NODDI and DTI metrics at each ROI was done using the independent t-test. Significant values were taken at $p<0.05$. Data analysis for demographic data and S-NAB scores was done using the independent t-test. Data were analysed between HC, REC and NREC groups.

RESULTS

Demographics

At three months post-mTBI diagnosis, a total of 57 mTBI subjects and 10 healthy individuals (HC) were recruited for the study. 16 patients were categorised as recovered (REC) and 41 as non-recovered (NREC) based on the S-NAB scores. The mean age of participants was 28.40 (HC), 28.56 (REC) years, and 28.17 (NREC) years. There were 48 (71.6%) male and 19 (28.4%) female participants. There was no significant difference in age and schooling years between HC, REC and NREC groups (Table 1).

Neuropsychological assessment outcomes

There were significantly ($p<0.05$) reduced attention and language domain scores in the NREC group compared to the HC group at 3 months. On the other hand, REC group had unimpaired S-NAB scores. Comparing REC versus NREC groups, the NREC group had reduced attention and visuospatial domain scores although the overall visuospatial score of NREC was considered unimpaired (Table 1).

DTI and NODDI ROI-based analyses between HC vs. REC, HC vs. NREC and REC vs. NREC at 3 months post-injury

Neurite density index (NDI)

NDI was reduced in REC versus HC at the right (0.567 vs. 0.601, $p=0.023$) and left (0.563 vs. 0.606, $p=0.010$) cingulate gyri, right (0.426 vs. 0.465, $p=0.041$) and left (0.403 vs. 0.447, $p=0.003$) hippocampi as well as the right superior fronto-occipital fasciculus (0.678 vs 0.746, $p=0.023$). NDI was also reduced in REC compared to NREC at the right superior fronto-occipital fasciculus (0.678 vs. 0.722, $p=0.036$), right (0.426 vs. 0.454, $p=0.010$) and left (0.403 vs. 0.439, $p<0.001$) hippocampi (Figure 2).

Orientation dispersion index (ODI)

At the left superior cerebellar peduncle, ODI was increased in REC versus HC (0.176 vs. 0.149, $p=0.038$) and NREC versus HC (0.181 vs. 0.149, $p=0.019$). At the left inferior cerebellar peduncle, ODI was increased in NREC versus HC (0.234 vs. 0.219, $p=0.026$). At the pontine crossing tract, ODI was reduced in REC versus NREC (0.175 vs. 0.188, $p=0.022$), however ODI was increased in REC versus NREC at the left medial lemniscus (0.133 vs. 0.124, $p=0.025$) and anterior limb of the left internal capsule (0.153 vs. 0.145, $p=0.030$) (Figure 3).

Isotropic volume fraction (ISOVF)

There was reduced ISOVF in REC versus HC at the splenium of corpus callosum (0.186 vs. 0.222, $p=0.011$), posterior limb of left internal capsule (0.085 vs. 0.101, $p=0.038$) and left cingulate gyrus (0.111 vs. 0.164, $p=0.023$). Reduced ISOVF was also seen in NREC versus HC at the posterior limb of left internal capsule (0.082 vs. 0.101, $p=0.018$) and left cingulate gyrus (0.117 vs. 0.164, $p=0.007$). Increased ISOVF was seen in REC versus NREC at the right external capsule

Table 1: Demographic data and neuropsychological assessment at 3 months post-trauma (*score of ≤85 is considered impaired cognition)

Demographic Data						
Criteria	**HC**	**REC**	**NREC**	**p-value**		
				HC vs REC	**HC vs NREC**	**REC vs NREC**
N	10	16	41			
Mean age (years)	28.40 ± 6.84	25.86 ± 8.57	28.17 ± 9.00	0.960	0.940	0.882
Gender (M/F)	2:1	2:1	3:1			
Mean Years of Education	13.80 ± 1.55	12.93 ± 2.10	12.79 ± 2.02	0.275	0.148	0.811
Neuropsychological Assessment						
S-NAB Score (mean)	**HC**	**REC**	**NREC**	**p-value (⁺ indicates p<0.05)**		
				HC vs REC	**HC vs NREC**	**REC vs NREC**
Attention Baseline/ 3 months	98.80 ± 20.20	88.43/101.19 ± 12.24	76.78/85.14 ± 16.14	0.709	0.027⁺	0.001⁺
Language Baseline/ 3 months	93.00 ± 14.06	92.31/86.00 ± 20.21	84.06/*77.56 ± 19.59	0.348	0.023⁺	0.153
Memory Baseline/ 3 months	108.30 ± 10.67	99.25/105.69 ± 13.37	91.50/98.17 ± 12.63	0.607	0.024	0.052
Visuospatial Baseline/ 3 months	114.20 ± 13.01	108.00/108.25 ± 13.06	99.06/100.27 ± 13.63	0.588	0.005⁺	0.049
Executive Function Baseline/ 3 months	90.10 ± 14.75	88.75/90.63 ± 13.35	76.31/*83.51 ± 15.83	0.926	0.238	0.118
Total Screening Index Baseline/ 3 months	100.20 ± 12.11	93.19/97.25 ± 14.67	78.39/*82.49 ± 11.27	0.600	<0.001⁺	<0.001⁺

(0.072 vs. 0.053, p=0.012) and left fornix (0.135 vs. 0.098, p=0.020) (Figure 4).

Fractional anisotropy (FA)

There was reduced FA in REC versus HC (0.388 vs. 0.410, p=0.036) at the right cingulate gyrus. (Figure 5).

Mean diffusivity (MD)

At the right superior fronto-occipital fasciculus, there was increased MD in REC versus HC (0.696 vs 0.663, p=0.030). At the right cerebral peduncle, there was increased MD in NREC compared to HC (0.809 vs 0.783, p=0.010). Increased MD was seen in REC versus NREC at the middle cerebellar peduncle (0.715 vs. 0.706, p=0.042) and left external capsule (0.788 vs. 0.774, p=0.041) (Figure 6).

DISCUSSION

In this study, multiple cognitive domain deficits were detected in a proportion of the mTBI population (NREC) three months after injury. The impaired domains were consistent with

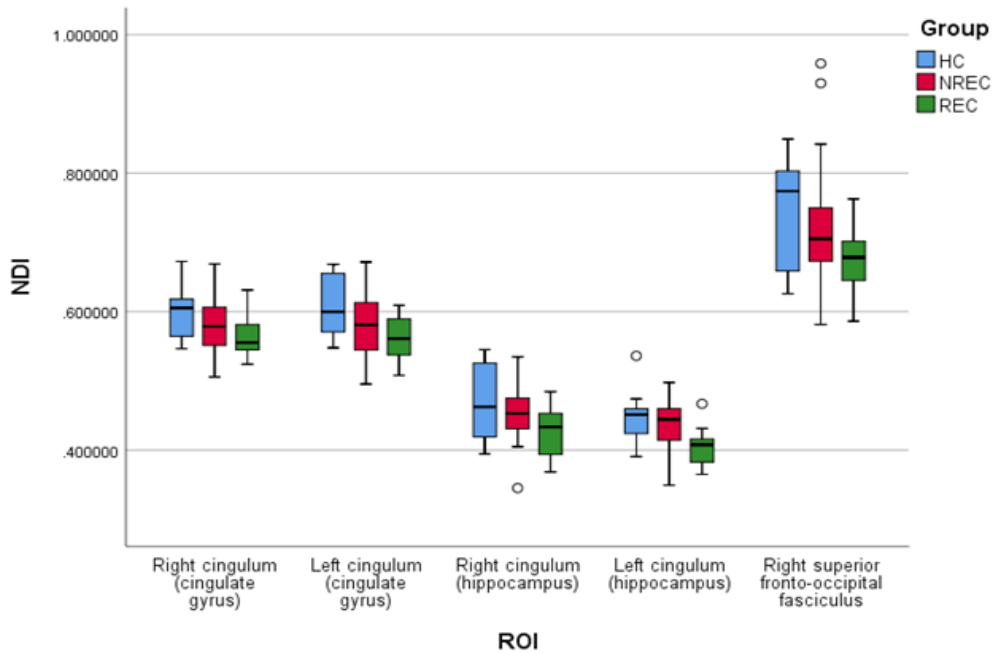

Figure 2. Comparisons of NDI between HC, REC and NREC according to ROI.

other reported TBI studies.[3,7,31] Several studies have also stated significant correlations between chronic TAI in mTBI and poor cognitive functional outcomes.[13,32] Our DTI and NODDI findings potentially explained the persistence of symptoms that may have otherwise be attributed to other causes. In this study, a subset of mTBI individuals had also improved their neurocognitive functioning over time to normalized neuropsychological domains score

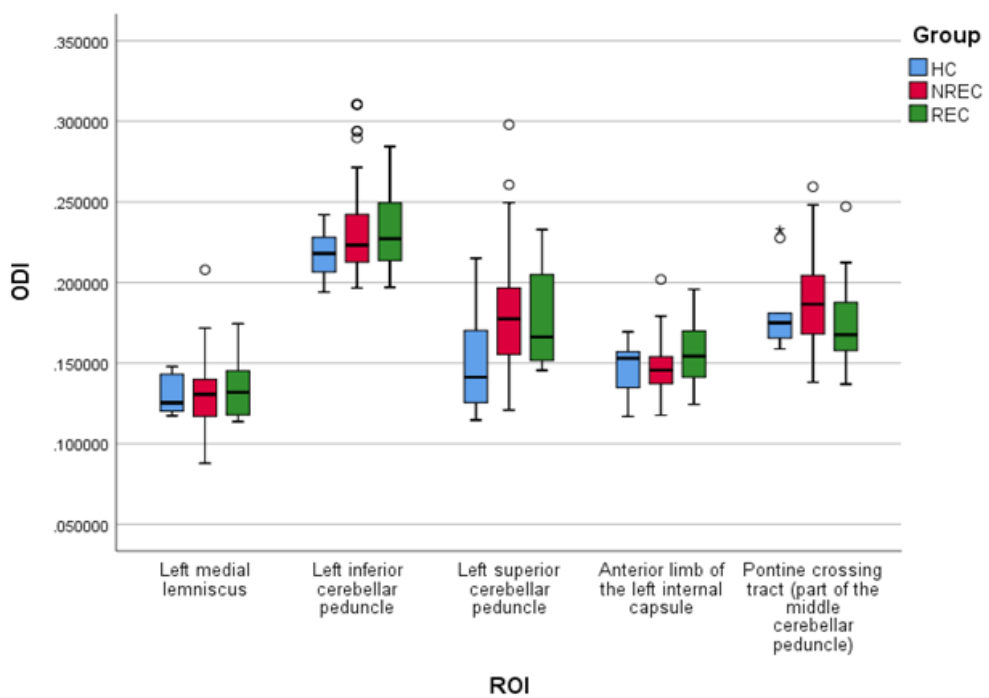

Figure 3. Comparisons of ODI between HC, REC and NREC according to ROI

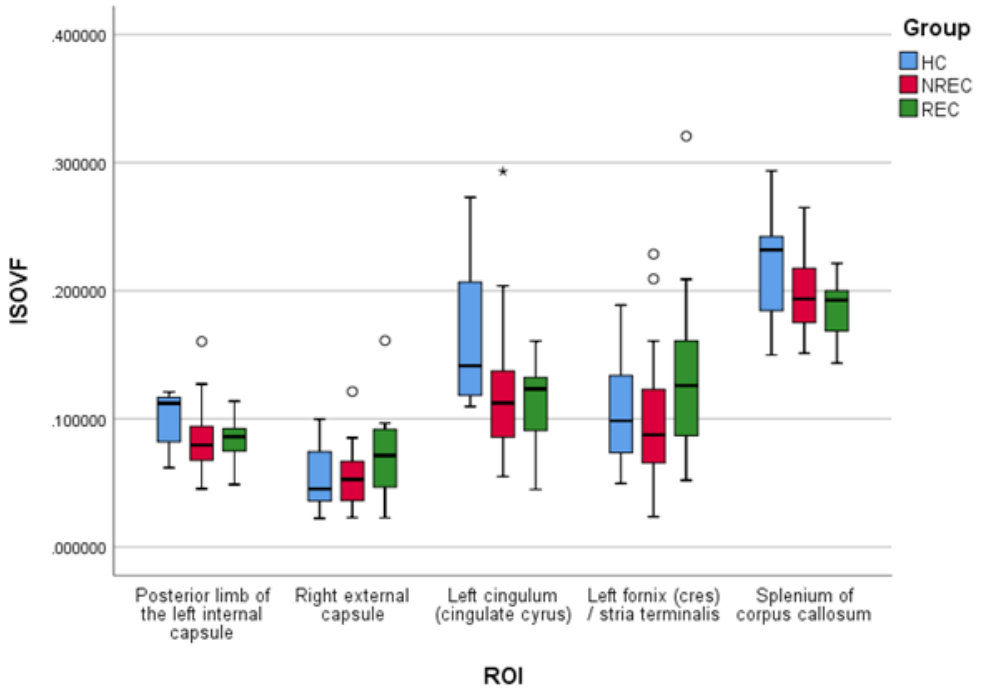

Figure 4. Comparisons of ISOVF between HC, REC and NREC according to ROI

values (REC).

Our study demonstrated that NODDI metrics (ODI, NDI, and ISOVF) detected more ROI changes than DTI metrics (FA and MD) at three months. This was consistent with previous studies which stated that the more anatomical WMT microstructure model of NODDI, was superior to DTI in detecting WMT changes.[16,18,20]

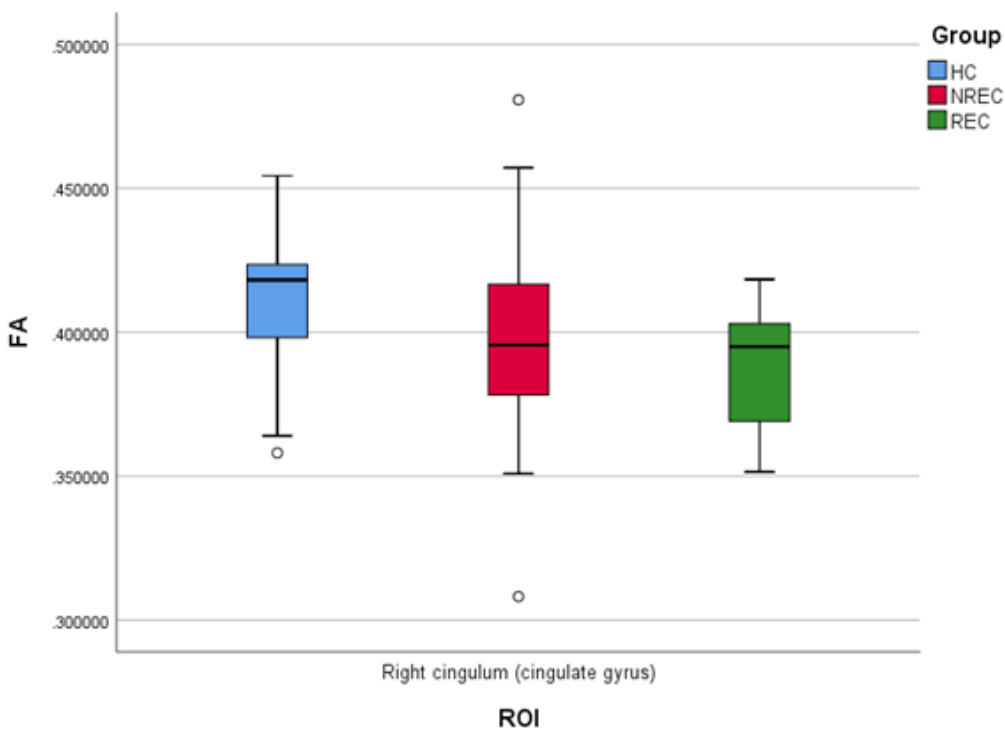

Figure 5. Comparisons of FA between HC, REC and NREC according to ROI

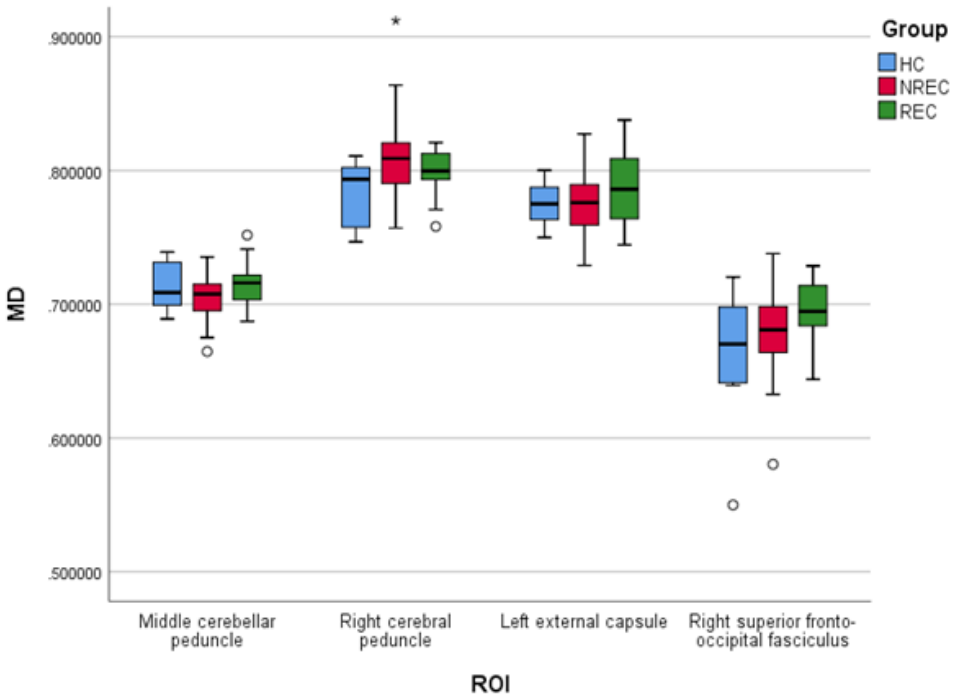

Figure 6. Comparisons of ODI between HC, REC and NREC according to ROI

Furthermore, NODDI, with its tri-compartmental model of diffusion, allowed us to hypothesise the underlying processes occurring in the brain post-mTBI.[16,33]

The affected ROIs consisted of projection fibres - posterior limbs of the internal capsule and cerebellar peduncles; association fibres - cingulum and fronto-occipital fasciculus, and the splenium of the corpus callosum; all commonly affected tracts in diffusion MRI studies on TBI.[14]

REC group showed lower NDI compared to HC and NREC groups at multiple WMTs. When taken together, the mTBI group demonstrated significantly lower NDI post-injury compared to HC, suggesting axonal degeneration or apoptosis.[15,34,35]

Reduced NDI in bilateral cingulate gyri, bilateral hippocampi, and the right superior fronto-occipital fasciculus in REC suggested persistent axonal injury or degeneration at three months post-trauma.[34] This correlates with other literature, which shows reduced white matter integrity in the early phase of injury[36] and a serial decline in NDI in the first six months post-mTBI.[4] No significant difference in NDI was found between NREC and HC cohorts, potentially indicating ongoing changes. Another study of concussed athletes who underwent diffusion MRI at a median of 24 months post-trauma reported an increase in NDI, most likely due to axonal proliferation.[19] However, in the still-recovering NREC group, we postulate that another concurrent process was occurring, which caused the NREC group to have NDI higher than REC and not significantly different NDI to HC despite having impaired cognition.

Both REC and NREC groups showed increased ODI than HC at the left superior and inferior cerebellar peduncles (NREC), indicating increased neurite dispersion and reducing fibre coherence, at the affected ROIs at three months post-trauma. This is comparable to the ODI results of other studies involving mTBI.[15,20,37] ODI was increased in REC compared to NREC at two ROIs but reduced in REC compared to NREC in another ROI, giving no clear trend. Increased dispersion with the absence of significant change in neurite density and oedema may represent gliosis.[38]

Reduced ISOVF was seen in both REC and NREC versus HC at multiple WMTs. ISOVF represents the water molecules outside of the neurite[16], suggesting reduced CSF or free water compartment surrounding neurites at 3 months post-trauma, with a similar relationship between mTBI and non-mTBI seen in another study.[15] ISOVF was also reduced at several ROIs in NREC compared to REC.

Lower FA may represent either reduced neurite density or degradation of fibre integrity.[39] In our

Table 2: Comparison for NODDI and DTI between HC, REC and NREC according to ROI

White Matter Tract (ROI)	μ HC	μ REC	μ NREC	Significant differences ($p < 0.05$)
Neurite density tndex (NDI)				
Right cingulum (cingulate gyrus) (T35)	0.601 ± 0.040	0.566 ± 0.033	0.583 ± 0.043	HC vs. REC
Left cingulum (cingulate gyrus) (T36)	0.606 ± 0.045	0.563 ± 0.033	0.579 ± 0.043	HC vs. REC
Right cingulum (hippocampus) (T37)	0.465 ± 0.056	0.426 ± 0.037	0.454 ± 0.036	HC vs. REC REC vs. NREC
Left cingulum (hippocampus) (T38)	0.447 ± 0.041	0.403 ± 0.026	0.439 ± 0.035	HC vs. REC REC vs. NREC
Right superior fronto-occipital fasciculus (T43)	0.746 ± 0.078	0.678 ± 0.047	0.722 ± 0.075	HC vs. REC REC vs. NREC
Orientation dispersion index (ODI)				
Pontine crossing tract (part of middle cerebellar peduncle) (T2)	0.183 ± 0.026	0.175 ± 0.027	0.188 ± 0.021	REC vs. NREC
Left medial lemniscus (T10)	0.131 ± 0.012	0.133 ± 0.018	0.124 ± 0.017	REC vs. NREC
Left inferior cerebellar peduncle (T12)	0.219 ± 0.015	0.234 ± 0.032	0.235 ± 0.032	HC vs. NREC
Left superior cerebellar peduncle (T14)	0.149 ± 0.031	0.176 ± 0.030	0.181 ± 0.039	HC vs. REC HC vs. NREC
Anterior limb of left internal capsule (T18)	0.148 ± 0.016	0.153 ± 0.018	0.145 ± 0.013	REC vs. NREC
Isotropic volume fraction (ISOVF)				
Splenium of corpus callosum (T5)	0.222 ± 0.044	0.186 ± 0.023	0.200 ± 0.032	HC vs. REC
Posterior limb of left internal capsule (T22)	0.101 ± 0.022	0.085 ± 0.015	0.082 ± 0.022	HC vs. REC HC vs. NREC
Right external capsule (T33)	0.056 ± 0.026	0.072 ± 0.034	0.053 ± 0.021	REC vs. NREC
Left cingulum (cingulate gyrus) (T36)	0.164 ± 0.059	0.111 ± 0.030	0.117 ± 0.045	HC vs. REC HC vs. NREC
Left fornix (cres) / stria terminalis (T40)	0.107 ± 0.042	0.135 ± 0.067	0.098 ± 0.045	REC vs. NREC
Fractional anisotropy (FA)				
Right cingulum (cingulate gyrus) (T35)	0.410 ± 0.030	0.388 ± 0.021	0.398 ± 0.032	HC vs. REC
Mean diffusivity (MD)				
Middle cerebellar peduncle (T1)	0.713 ± 0.017	0.715 ± 0.016	0.706 ± 0.015	REC vs. NREC
Right cerebral peduncle (T15)	0.783 ± 0.025	0.799 ± 0.018	0.809 ± 0.027	HC vs. NREC
Left external capsule (T34)	0.7776 ± 0.017	0.788 ± 0.028	0.774 ± 0.021	REC vs. NREC
Right superior fronto-occipital fasciculus (T43)	0.663 ± 0.048	0.696 ± 0.023	0.680 ± 0.029	HC vs. REC

study, FA yielded one significant ROI where lower FA was seen in REC vs HC at the right cingulate gyrus. Lower NDI in REC at the same ROI explains this reduced FA was due to axonal loss.

MD was increased in the right superior fronto-occipital fasciculus (SFOF) and right cerebral peduncle in REC and NREC groups, respectively, compared to HC. Increased MD may represent reduced axonal density, alterations in fibre orientation, reduced fibre integrity, and is further confounded with CSF content in the voxel.[20] Correlating with NDI findings at the right SFOF, the increased MD can be attributed to reduced neurite density.

Despite having higher NDI than REC, NREC demonstrated impaired cognition. We postulate that there may have been concurrent reactive astrogliosis in both groups, which was more abundant in NREC resulting in higher NDI. Additionally, there was no significant difference of NDI between NREC and HC despite the expected loss of neurite density post-trauma. The lack of significant difference of FA between NREC and HC was consistent with the NDI findings. The increased ODI, and increased MD values supported this postulation.[13,38]

Recent literature reported differing outcomes for NDI parameters in chronic mTBI populations. One study showed a serial decline in NDI in the first 6 months post-trauma.[4] On the other hand, two studies on athletes with chronic concussion showed increased NDI compared to non-concussed subjects, which are postulated to be due to either neuroinflammation and axonal swelling, neuroplasticity or increased proliferation of microglia.1[9,37,40] However, these studies did not further analyse the outcome between cognitively recovered and non-recovered subjects. Our findings show that the REC group has different NODDI and DTI findings compared to the NREC group.

The limitations of this study were first, the recruitment of healthy controls was done after patient recruitment to match the mTBI group in demographics and years of education. Unfortunately, this yielded only 10 subjects due to Covid restrictions. Second, although we performed a standard EPI correction in our methodology, we did not perform reverse-encoding data.

In conclusion, NODDI detects more WMT microstructural changes in mTBI than DTI. The added microstructural changes elucidated by NODDI add to the armamentarium of understanding the pathophysiological changes occurring in the neuro-recovery process.

Based on our NODDI findings of lower NDI in the overall mTBI cohort, lower NDI in REC but not NREC versus HC, increased ODI and correlating with the DTI results, we postulate that at three months post-mTBI, there is concurrent axonal degeneration and astrogliosis, with a more extensive gliotic process in NREC compared to REC. In addition, the significantly affected WMTs in our study are comparable to those seen in previous diffusion MRI studies on mTBI.

Further longitudinal studies involving NODDI are essential to improve our understanding of mild traumatic brain injury recovery. It is hoped that in the future, with an enhanced understanding of these changes in NODDI, there is a potential for detecting mTBI patients at risk of having cognitive impairment, thus pre-empting early cognitive rehabilitation.

DISCLOSURE

Ethics: This study was approved by the University Malaya Research Ethics Committee (UMREC) (MECID No: 2018315-6133).

Financial support: Prasath Swaminathan and Norlisah Ramli were supported by Malaysian Ministry of Science, Technology and Innovation (MOSTI).

Conflict of interest: None

REFERENCES

1. Puvanachandra P, Hyder AA. The burden of traumatic brain injury in Asia: a call for research. *Pak J Neurol Sci* 2009;4(1):27-32.
2. Katz D, Cohen S, Alexander M. Mild traumatic brain injury. *Handb Clin Neuro*l 2015;127:131-56. doi: 10.1016/B978-0-444-52892-6.00009-X
3. Carroll LJ, Cassidy JD, Cancelliere C, *et al*. Systematic review of the prognosis after mild traumatic brain injury in adults: cognitive, psychiatric, and mortality outcomes: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil* 2014;95(3):S152-S73. doi:10.1016/j.apmr.2013.08.300
4. Palacios E, Owen JP, Yuh EL, *et al*. The evolution of white matter changes after mild traumatic brain injury: A DTI and NODDI study. *BioRxiv* 2018:345629. doi:10.1101/345629
5. Hamzah N, Muhamad NA, Hariri F, Mazlan M, Ramli N, Narayanan V. A short-term longitudinal study on multi dimensional outcomes following mild traumatic brain injury in multi-ethnic Malaysia. *J Health Transl Med* 2021;24(2):1-10. doi: 10.22452/jummec.vol24no2.1
6. Marshall S, Bayley M, McCullagh S, Berrigan L, Fischer L, Ouchterlony D. Guidelines for concussion

/mild traumatic brain injury and prolonged symptoms. *Ontario Neurotrauma Foundation* 2018: URL: https://onf.org/3rd-edition-guidelines-for-concussion-mild-traumatic-brain-injury-and-persistent-symptoms/
7. Cicerone KD, Goldin Y, Ganci K, *et al*. Evidence-based cognitive rehabilitation: systematic review of the literature from 2009 through 2014. *Arch Phys Med Rehabil* 2019;100(8):1515-33. doi: 10.1016/j.apmr.2019.02.011
8. American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury. *J Head Trauma Rehabil* 1993;8(3):86-7.
9. De Kruijk JR, Twijnstra A, Leffers P. Diagnostic criteria and differential diagnosis of mild traumatic brain injury. *Brain Inj* 2001;15(2):99-106. doi: 10.1080/02699050119160
10. Inglese M, Makani S, Johnson G, *et al*. Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *J Neurosurg* 2005;103(2):298-303. doi: 10.3171/jns.2005.103.2.0298
11. Wallace EJ, Mathias JL, Ward L. Diffusion tensor imaging changes following mild, moderate and severe adult traumatic brain injury: a meta-analysis. *Brain Imaging Behav* 2018;12(6):1607-21. doi: 10.1007/s11682-018-9823-2
12. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. *Neurotherapeutics* 2007;4(3):316-29. doi: 10.1016/j.nurt.2007.05.011
13. Veeramuthu V, Narayanan V, Tan LK, *et al*. Diffusion tensor imaging parameters in mild traumatic brain injury and its correlation with early neuropsychological impairment: a longitudinal study. *J Neurotrauma* 2015;32(19):1497-509. doi: 10.1089/neu.2014.3750
14. Hulkower M, Poliak D, Rosenbaum S, Zimmerman M, Lipton ML. A decade of DTI in traumatic brain injury: 10 years and 100 articles later. *Am J Neuroradiol* 2013;34(11):2064-74. doi: 10.3174/ajnr.A3395
15. Oehr LE, Yang JY-M, Chen J, Maller JJ, Seal ML, Anderson JFI. Investigating white matter tract microstructural changes at six–twelve weeks following mild traumatic brain injury: A combined diffusion tensor imaging and neurite orientation dispersion and density imaging study. *J Neurotrauma* 2020;38(16):2255-63. doi: 10.1089/neu.2020.7310
16. Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. *Neuroimage* 2012;61(4):1000-16. doi: 10.1016/j.neuroimage.2012.03.072
17. Wallace EJ, Mathias JL, Ward L, Fripp J, Rose S, Pannek K. A fixel-based analysis of micro- and macro-structural changes to white matter following adult traumatic brain injury. *Hum Brain Mapp* 2020;41(8):2187-97. doi: 10.1002/hbm.24939
18. Timmers I, Roebroeck A, Bastiani M, Jansma B, Rubio-Gozalbo E, Zhang H. Assessing microstructural substrates of white matter abnormalities: a comparative study using DTI and NODDI. *PloS One* 2016;11(12). doi: 10.1371/journal.pone.0167884
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* 2017;38(8):4201-11. doi: 10.1002/hbm.23658
20. 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* 2019;40(6):1908-18. doi: 10.1002/hbm.24500
21. Mott T, McConnon ML, Rieger BP. Subacute to chronic mild traumatic brain injury. *Am Fam Physician* 2012;86(11):1045-51.
22. van der Naalt J, Timmerman ME, de Koning ME, *et al*. Early predictors of outcome after mild traumatic brain injury (UPFRONT): an observational cohort study. *Lancet Neurol* 2017;16(7):532-40. doi: 10.1016/S1474-4422(17)30117-5
23. De Koning ME, Scheenen ME, Van Der Horn HJ, Spikman JM, Van Der Naalt J. From 'miserable minority' to the 'fortunate few': the other end of the mild traumatic brain injury spectrum. *Brain Inj* 2018;32(5):540-3. doi: 10.1080/02699052.2018.1431844
24. White T, Stern RA. NAB, neuropsychological assessment battery: Psychometric and technical manual: Psychological Assessment Resources; 2003.
25. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. *NeuroImage* 2012;62(2):782-90. doi: 10.1016/j.neuroimage.2011.09.015
26. Daducci A, Canales-Rodríguez EJ, Zhang H, Dyrby TB, Alexander DC, Thiran J-P. Accelerated microstructure imaging via convex optimization (AMICO) from diffusion MRI data. *NeuroImage* 2015;105:32-44. doi: 10.1016/j.neuroimage.2014.10.026
27. Smith SM, Jenkinson M, Johansen-Berg H, *et al*. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 2006;31(4):1487-505. doi:10.1016/j.neuroimage.2006.02.024
28. Mori S, Oishi K, Jiang H, *et al*. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *NeuroImage* 2008;40(2):570-82. doi: 10.1016/j.neuroimage.2007.12.035
29. Oishi K, Zilles K, Amunts K, *et al*. Human brain white matter atlas: Identification and assignment of common anatomical structures in superficial white matter. *NeuroImage* 2008;43(3):447-57. doi: 10.1016/j.neuroimage.2008.07.009
30. 2017. ICR. IBM SPSS statistics for windows, Version 25.0. Armonk, NY: IBM Corp.
31. Ponsford J, Bayley M, Wiseman-Hakes C, *et al*. INCOG recommendations for management of cognition following traumatic brain injury, part II: attention and information processing speed. *J Head Trauma Rehabil* 2014;29(4):321-37. doi: 10.1097/HTR.0000000000000072
32. Shenton ME, Hamoda HM, Schneiderman JS, *et al*. A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. *Brain Imaging Behav* 2012;6(2):137-92. doi: 10.1007/s11682-012-9156-5
33. Kamiya K, Hori M, Aoki S. NODDI in clinical research. *J Neurosci Methods* 2020;346:108908. doi: 10.1016/j.jneumeth.2020.108908

34. Armstrong RC, Mierzwa AJ, Marion CM, Sullivan GM. White matter involvement after TBI: Clues to axon and myelin repair capacity. *Exp Neurol* 2016;275 Pt 3:328-33. doi:10.1016/j.expneurol.2015.02.011
35. Wu YC, Mustafi SM, Harezlak J, Kodiweera C, Flashman LA, McAllister TW. Hybrid diffusion imaging in mild traumatic brain injury. *J Neurotrauma* 2018;35(20):2377-90. doi: 10.1089/neu.2017.5566
36. Stenberg J, Eikenes L, Moen KG, Vik A, Håberg AK, Skandsen T. Acute diffusion tensor and Kurtosis imaging and outcome following mild and traumatic brain injury. *J Neurotrauma* 2021. doi: 10.1089/neu.2021.0074
37. Mayer AR, Ling JM, Dodd AB, Meier TB, Hanlon FM, Klimaj SD. A prospective microstructure imaging study in mixed-martial artists using geometric measures and diffusion tensor imaging: methods and findings. *Brain Imaging Behav* 2017;11(3):698-711. doi:10.1007/s11682-016-9546-1
38. Yi SY, Barnett BR, Torres-Velázquez M, *et al*. Detecting microglial density with quantitative multi-compartment diffusion MRI. *Front Neurosci* 2019;13:81. doi: 10.3389/fnins.2019.00081
39. Roberts TP, Liu F, Kassner A, Mori S, Guha A. Fiber density index correlates with reduced fractional anisotropy in white matter of patients with glioblastoma. *Am J Neuroradiol* 2005;26(9):2183-6.
40. Caron B, Bullock D, Kitchell L, *et al*. Human white matter microstructure predicts elite sports participation. 2020. DOI: 10.31234/osf.io/dxaqp

APPENDIX:

Table A1: International Consortium of Brain Mapping (ICBM) Labels for ROIs.

ROI	Code	Label (White Matter Tract)
T0	NULL	Null (background)
T1	MCP	Middle cerebellar peduncle
T2	PCT	Pontine crossing tract (a part of MCP)
T3	GCC	Genu of corpus callosum
T4	BCC	Body of corpus callosum
T5	SCC	Splenium of corpus callosum
T6	FX	Fornix (column and body of fornix)
T7	CST-R	Corticospinal tract right
T8	CST-L	Corticospinal tract left
T9	ML-R	Medial lemniscus right
T10	ML-L	Medial lemniscus left
T11	ICP-R	Inferior cerebellar peduncle right
T12	ICP-L	Inferior cerebellar peduncle left
T13	SCP-R	Superior cerebellar peduncle right
T14	SCP-L	Superior cerebellar peduncle left
T15	CP-R	Cerebral peduncle right
T16	CP-L	Cerebral peduncle left
T17	ALIC-R	Anterior limb of internal capsule right
T18	ALIC-L	Anterior limb of internal capsule left
T19	PLIC-R	Posterior limb of internal capsule right
T20	PLIC-L	Posterior limb of internal capsule left
T21	RLIC-R	Retrolenticular part of internal capsule right
T22	RLIC-L	Retrolenticular part of internal capsule left
T23	ACR-R	Anterior corona radiata right
T24	ACR-L	Anterior corona radiata left
T25	SCR-R	Superior corona radiata right
T26	SCR-L	Superior corona radiata left
T27	PCR-R	Posterior corona radiata right
T28	PCR-L	Posterior corona radiata left
T29	PTR-R	Posterior thalamic radiation (include optic radiation) right
T30	PTR-L	Posterior thalamic radiation (include optic radiation) left
T31	SS-R	Sagittal stratum (include inferior longitidinal fasciculus and inferior fronto-occipital fasciculus) right
T32	SS-L	Sagittal stratum (include inferior longitidinal fasciculus and inferior fronto-occipital fasciculus) left
T33	EC-R	External capsule right
T34	EC-L	External capsule left
T35	CGC-R	Cingulum (cingulate gyrus) right
T36	CGC-L	Cingulum (cingulate gyrus) left
T37	CGH-R	Cingulum (hippocampus) right
T38	CGH-L	Cingulum (hippocampus) left
T39	FX/ST-R	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) right
T40	FX/ST-L	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) left
T41	SLF-R	Superior longitudinal fasciculus right

T42	SLF-L	Superior longitudinal fasciculus left
T43	SFO-R	Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) right
T44	SFO-L	Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) left
T45	IFO-R	Inferior fronto-occipital fasciculus right
T46	IFO-L	Inferior fronto-occipital fasciculus left
T47	UNC-R	Uncinate fasciculus right
T48	UNC-L	Uncinate fasciculus left
T49	TAP-R	Tapatum right
T50	TAP-L	Tapatum left

Each ROI corresponds to a WMT Label