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Research article

Myelin water fraction decrease in individuals with chronic mild traumatic brain injury and persistent symptoms

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ABSTRACT

The diffuse and continually evolving secondary changes after mild traumatic brain injury (mTBI) make it challenging to assess alterations in brain-behaviour relationships. In this study we used myelin water imaging to evaluate changes in myelin water fraction (MWF) in individuals with chronic mTBI and persistent symptoms and measured their cognitive status using the NIH Toolbox Cognitive Battery. Fifteen adults with mTBI with persistent symptoms and twelve age, gender and education matched healthy controls took part in this study. We found a significant decrease in global white matter MWF in patients compared to the healthy controls. Significantly lower MWF was evident in most white matter region of interest (ROIs) examined including the corpus callosum (separated into genu, body and splenium), minor forceps, right anterior thalamic radiation, left inferior longitudinal fasciculus; and right and left superior longitudinal fasciculus and corticospinal tract. Although patients showed lower cognitive functioning, no significant correlations were found between MWF and cognitive measures. These results suggest that individuals with chronic mTBI who have persistent symptoms have reduced MWF.

1. Introduction

Mild traumatic brain injury (mTBI) is an urgent public health concern. A systematic review from the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury indicated a hospital treatment rate of 100–300 mTBIs per 100,000 people but a predicted incidence of 600 per 100,000 people [1]. mTBI caused either by a direct blow to the head, face, neck, or elsewhere on the body that leads to an impulsive force transmitted to the head induce subtle, transient, and spatially distributed changes in brain structure and function, resulting in cognitive, emotional and behavioral challenges. While most individuals recover within 10–14 days, approximately 20% will experience persistent symptoms for months or years after injury [2]. Stress, anxiety and emotional distress are important risk factor for long-term impairment. Symptom persistence is therefore a consequence of an interaction between neurological and psychosocial factors and the associated health outcomes. Despite its high prevalence, the mechanisms underlying mTBI remain elusive.

The diffuse and continually evolving secondary changes that are the hallmark of traumatic mTBI have made it challenging to evaluate brain-behaviour relationships. Neurodegeneration is linked with TBI [3], however conventional neuroimaging tools (such as CT and routine clinical MRI) cannot detect the widespread and often subtle changes in structure and function that occur in the brain [4]. The long-term effects of mTBI are less clear than more severe head injuries and neuroimaging findings are less consistent [5, 6]. Thus advanced MRI techniques are increasingly being used to examine and monitor changes in the brain following mTBI [7, 8, 9].

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Table 1. Description and demographics of participants with mTBI.

Subject	Approx. Time Since Injury (years)	Age (years)	Gender	Years of Education	Injury Type
S1	2	18	F	12	Sport
S2	1	18	M	13	Multiple Concussions
S3	1	22	M	17	Fall
S4	6 months	29	M	16	Sport
S5	7 months	29	M	16	Multiple Concussions
S6	1	34	F	16	Sport
S7	4	34	F	18	MVA
S8	2	35	M	14	Assault
S9	2	43	F	18	MVA
S10	2	45	M	16	Multiple Concussions
S11	2.5	48	F	15	Assault
S12	9 months	48	M	16	Sport
S13	5	48	F	14	Multiple Concussions
S14	1.5	57	F	14.5	Fall
S15	1	50	M	17	Fall

MVA – motor vehicle accident (single incident).

Physiologically, movement of the brain within the skull causes shearing/stretching of the axons and initiates a cascade of molecular events which disrupts normal brain cell function. Metabolic changes occur rapidly following axonal strain, altering the permeability of sodium channels, resulting in an increase in intra-axonal calcium and ultimately a failure of the sodium pump, causing further metabolic disruptions [10]. Long white matter tracts and the corpus callosum are particularly vulnerable to these forces and diffuse axonal injury (DAI) can lead to demyelination and axonal loss resulting in brain atrophy [11, 12, 13, 14, 15, 16]. Loss of myelin increases axonal vulnerability to further trauma and may predispose the axon to further damage [17, 18]. In animal models of mTBI, extensive demyelination is reported [19, 20], and human post mortem studies have found evidence of loss of myelin [21] years after the initial TBI symptoms have resolved. Given the importance of the integrity of white matter tracts, a validated quantitative technique to examine myelination (loss and possible remyelination [17, 22]) of these tracts would provide a powerful approach to understand the pathology of TBI, the evolving nature of the injury and ultimately could be used to evaluate the impact of neurorehabilitation.

Measuring myelin *in vivo* using MR is nontrivial and requires specialized techniques [23, 24]. Myelin is a lipid rich membrane assembly that wraps around axons in a series of layers. Myelin enables saltatory conduction which produces fast and efficient neuronal signal transmission across the brain and throughout the body. The loss or disruption of myelin results in loss of saltatory conduction causing slower signal propagation and thus delay of translation of information. Measuring non-aqueous protons in myelin is difficult because the MR signal decays too rapidly to be measured by common MR techniques. The water trapped between myelin bilayers is known as myelin water and it is accessible using MR. Several different techniques have been developed to measure the myelin water [25], one such approach involves using multi-component T_2 analysis, myelin water imaging (MWI). Multi-component T_2 relaxation can be used to detect different water environments in human brain tissue [26, 27, 28], including a short T_2 component that is thought to be myelin water [29, 30, 31, 32, 33, 34, 35, 36, 37]. The proportion of water in brain that can be attributed to myelin water is known as the myelin water fraction (MWF) which can be used as a marker for myelin [38]. MWF has been validated as a myelin marker in histological studies in animal models [39, 40, 41] and human post-mortem Multiple Sclerosis (MS) brain [42, 43, 44] and spinal cord [45]. MWF has been found to be decreased in normal appearing white matter in neurodegenerative diseases such as MS [46, 47, 48, 49]. MWF has previously been shown to decrease post single sports concussion (mTBI) and then recover after 2 months [50], showing the utility of MWF in mTBI.

A few groups have documented a possible association between myelin water fraction and cognition. Recently, two studies in MS [51, 52] found correlations between heterogeneity in MWF in several ROIs (including the corpus callosum) and a number of cognitive tests including the Symbol Digit Modalities Test (SDMT) (a measure of cognitive processing speed) in MS but not in controls. Lang et al. [53] showed that, in patients with schizophrenia, frontal white matter correlated with scores on a premorbid IQ test, the North American Adult Reading Test (NAART). Similarly, Choi et. al [54]. found a significant correlation between Processing Speed Index and a global measure of apparent myelin water fraction in a group of moderate to severe TBI subjects 3 months post-injury. Although more research is needed to explore the potential cognitive sequelae of MWF changes, these findings suggest that myelin measures may reflect underlying cognitive functioning. However, to date the change in MWF in individuals with chronic mTBI who have persistent symptoms is unknown.

Here we examine myelin water fraction (MWF) within a group of chronic participants with mTBI who present with persistent symptoms and compare them to healthy controls using a whole cerebrum coverage MWF sequence to characterize differences in myelin. We hypothesized that brain myelin in mTBI would be reduced compared to that in controls. We also examined the effects of age and years of education on MWF, independent of mTBI. Finally, we compared cognitive scores between the two groups and their relationship with MWF. Based on previous results by Choi et al [55] we hypothesized that MWF would be particularly associated with processing speed and other measures of fluid cognitive abilities.

2. Materials and methods

2.1. Participants

Participants were recruited from brain injury associations across the Greater Vancouver area as part of a study to evaluate the impact of an intensive cognitive intervention program in adults with TBI [56]. All healthy controls were recruited from the lower mainland of Vancouver in close proximity to the university. All controls were screened to ensure that they had no history of head trauma, neuropsychiatric disorders, or any other neurological conditions. Participants with mTBI were excluded if they had a history of seizure, epilepsy, neurodegenerative disorder, major head trauma, or a psychiatric diagnosis. They were also excluded if they had severe vision or hearing impairment, have difficulty sitting in a

chair for 1 h or were medically unstable. Participants were also excluded if they were currently in litigation or if they had other severe medical conditions affecting brain function. They were also excluded if they had a diagnosis of psychiatric illness based on a Mini-international neuropsychiatric interview (MINI) [57]. The severity of injury was based on self-report using the diagnostic criteria from American Congress of Rehabilitation Medicine (ACRM) [58] and the World Health Organization (WHO) [59]. Information was retrospectively reported by the subjects, where mild TBI was defined as Loss of Consciousness (LOC) of less than 30 min and Post-traumatic amnesia (PTA) less than 24 h [58]. The study was approved by the Clinical Research Ethics Board at the University of British Columbia. All participants provided written consent according to the guidelines set by the Clinical Research Ethics Board. Subject demographics are given in Table 1, and individual subject mTBI demographics are given in Table 2. Time since injury varied from 6 months to 5 years post injury across subjects, and 6 months post-injury was determined to be the benchmark for identifying chronic mTBI [60].

2.2. MRI protocol

MRI scans were completed on a 3T Philips Achieva scanner. Sequences included a $3DT_1$ structural scan (MPRAGE TR = 3000 ms, TI = 1072 ms, $1 \times 1 \times 1mm^3$ voxel, 160 slices) for registration and segmentation of global white matter and white matter regions of interest (ROIs) and a 3D 48-echo Gradient and Spin Echo (GRASE) T_2 relaxation sequence with an EPI factor of 3 (TR = 1073, echo spacing = 8 ms, 20 slices acquired at $1 \times 2 \times 5$ mm and 40 slices reconstructed at $1 \times 1 \times 2.5$ mm, FOV $230 \times 190 \times 100$ mm, acquisition time 7.5 min) for MWF determination [61, 62] using the standard MR scanner reconstruction software.

2.3. Neuropsychological testing

The NIH Toolbox Cognition Battery [63] was used to evaluate cognition in both groups. The Test of Memory Malingering was used to exclude individuals showing suboptimal effort. Two primary composite cognitive measures were employed in this study [64]. The Crystallized composite score (age adjusted) from the NIH Toolbox was used to assess crystallized cognitive ability, which refers to an accumulated storage of verbal knowledge and skills that are heavily influenced by educational and cultural experience. The crystallized score was based on the average performance on the Picture Vocabulary Test (language) and Oral Reading Recognition Test (language). The Fluid composite score was based on performance on the following NIH Toolbox measures: Dimensional Change Card Sort Test (attention, executive function), Flanker Inhibitory Control and Attention Test (attention, executive function), Picture Sequence Memory Test (episodic memory), Pattern Comparison Processing Speed Test (processing speed), List Sorting Working Memory Test (working memory). Fluid ability is defined as the capacity for new learning and information processing in novel situations, which is especially influenced by biological processes and is less dependent on past exposure. All scores were age-adjusted based on the NIH Toolbox nationally representative U.S. normative sample, and standard scores had a mean of 100 and standard deviation of 15. Three healthy controls did not complete cognitive testing, one due to familiarity with the tests and two due to study retention loss.

2.4. Myelin water fraction (MWF) data analysis

The signal decay curve obtained by the T_2 relaxation sequence was modelled by multiple exponential components and the T_2 distribution was estimated using in-house software in matlab (MathWorks, Massachusetts, U.S.A) which contained a regularized non-negative least squares algorithm using the extended phase graph and flip angle estimation to deal with stimulated echo artifacts [26, 27, 28, 65, 66]. MWF in each image voxel was computed as the ratio of the area under the T_2 distribution with times of 10–40ms to the total area under the distribution. MWF and $3DT_1$ images were registered to MNI space and brain extracted and segmented using tools from FSL [67, 68, 69]. Slices below the inferior portion of the hypothalamus (mammillary body) were rejected in order to account for differing head sizes and make sure MWF was measured over the same brain coverage for all subjects. Global white matter (GWM) was segmented and pre-existing regions of interest from the JHU tract atlas in FSL [70, 71, 72] were used to segment specific tracts using FSL: splenium of corpus callosum (SCC), body of corpus callosum (BCC), genu of corpus callosum (GCC), minor forceps (MN), and right and left anterior thalamic radiation (ATR), inferior and superior longitudinal fasciculus (ILF and SLF respectively), and corticospinal tract (CST).

2.5. Statistical analysis

All statistical analysis was completed using IBM SPSS Statistics Version 25. Demographic differences were examined; age and education were compared between groups using an independent samples t-test and a chi-squared test was used to compare gender ratios between groups, where $p < 0.05$ was considered significant. Mean MWF for ROIs were compared between participant groups using an independent samples t-test, where $p < 0.05$ was considered significant. We elected not to correct for multiple comparisons because the limited sample size would require extremely large effects to detect statistical significance; therefore, a p-value set at $p < .05$ was deemed appropriate. In addition, we calculated Cohen's d effects sizes to provide information about the magnitude of the effects, which was deemed more important than paying attention to the associated p-values which are highly sensitive to sample size. Generally, Cohen's effect sizes of 0.2 are considered to be small, 0.5 medium, and 0.8 large in magnitude [73]. The association between age and years of education and MWF in each ROI was examined using Pearson's correlations (*r*) across controls and mTBI. A linear model comparing MWF (ANCOVA) across groups was used with age and education as covariates. Finally, cognitive scores were compared between groups using an independent sample's t-test and a Cohen's d to assess effect size. MWF was compared with cognitive scores in mTBI using Pearson's correlation.

3. Results

3.1. Demographic characteristics between groups

Tables 1 and 2 show the general group demographics and the demographic and clinical features for all the participants in this study. Age, education and gender were not significantly different between controls and individuals with mild TBI.

Table 2. Age and education in controls and participants with mTBI.

Subject Group	N	Gender Ratio (M:F)		Age (years) Mean ± sd (Range)		Education (years) Mean ± sd (Range)	
Control	12	8:4	$p = 0.5$	37.2 ± 12 (21–53)	$p = 0.6$	16.4 ± 3 (12–20)	$p = 0.2$
mTBI	15	8:7		37.2 ± 12 (18–57)		15.5 ± 2 (12–18)	

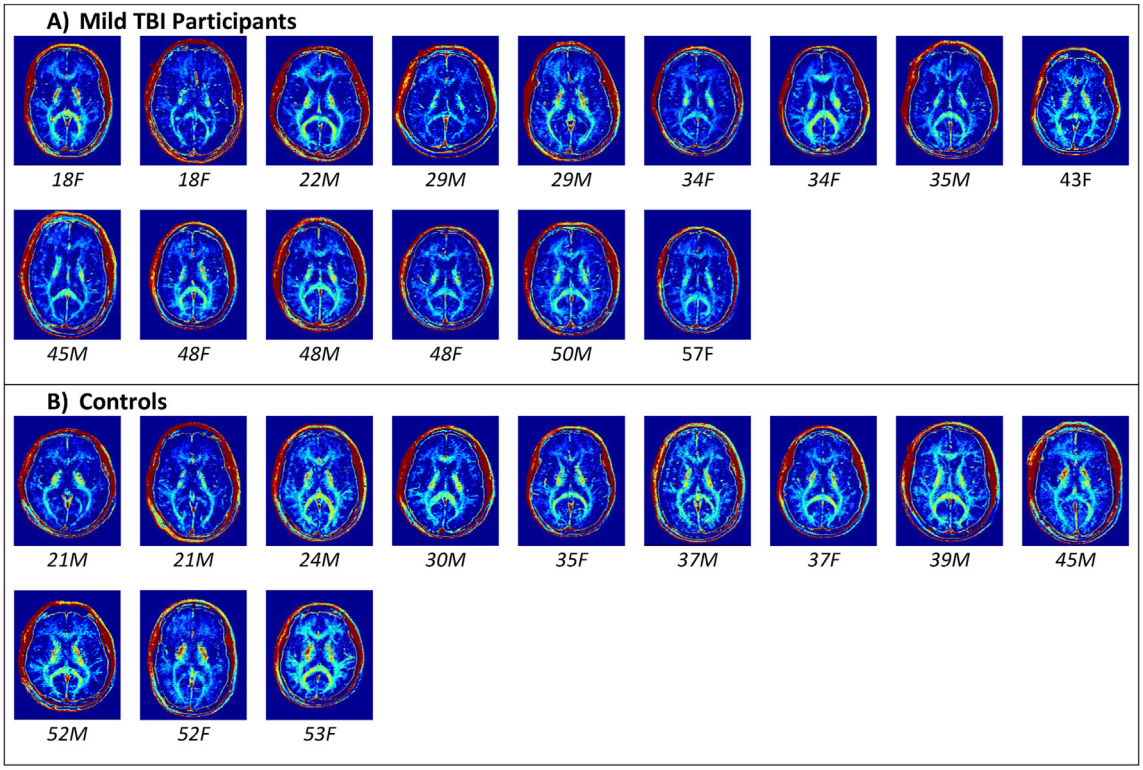

Figure 1. Myelin water fraction (MWF) maps for all participants; A) mild traumatic brain injury and B) controls with age and sex demographics.

Table 3. Mean and standard error of myelin water fraction (MWF) of all regions of interest; global white matter (GWM), splenium of corpus callosum (SCC), body of corpus callosum (BCC), genu of corpus callosum (GCC), anterior thalamic radiation (ATR), minor forceps (MN), inferior and superior longitudinal fasciculus (ILF and SLF respectively), corticospinal tract (CST) for controls and mTBI compared with an independent sample's t-test. No p-values survived Holm-Bonferroni analysis for multiple comparisons. Cohen's d was calculated as a measure of effect size.

Region of Interest		Control (n = 12)	Mild TBI (n = 15)	p-value	–Cohen's d
GWM		0.114 ± 0.005	0.101 ± 0.003	0.03	0.91
SCC		0.147 ± 0.006	0.125 ± 0.005	0.008	1.12
BCC		0.111 ± 0.006	0.095 ± 0.004	0.04	0.84
GCC		0.103 ± 0.005	0.086 ± 0.005	0.02	0.93
MN		0.087 ± 0.006	0.074 ± 0.003	0.04	0.83
ATR	Left	0.122 ± 0.006	0.107 ± 0.004	0.04	0.83
	Right	0.112 ± 0.006	0.097 ± 0.004	0.04	0.81
ILF	Left	0.100 ± 0.005	0.080 ± 0.005	0.008	1.12
	Right	0.133 ± 0.006	0.119 ± 0.003	0.04	0.82
SLF	Left	0.131 ± 0.005	0.115 ± 0.004	0.03	0.89
	Right	0.144 ± 0.006	0.126 ± 0.004	0.02	0.95
CST	Left	0.205 ± 0.006	0.188 ± 0.005	0.03	0.86
	Right	0.194 ± 0.006	0.176 ± 0.005	0.03	0.89

3.2. Myelin water fraction (MWF)

Figure 1 shows the MWF maps of all 15 participants with mTBI and 12 controls. Note the overall qualitative reduction in MWF in the mTBI participants. Region of interest (ROI) analysis confirmed significantly lower global white matter (GWM) MWF in the mTBI group compared to controls (see first row of Table 3 and Figure 2). Analysis of the ROIs showed a consistently lower MWF in the mTBI group compared with the controls in all ROIs (see Figure 2 and Table 3). Cohen's d were calculated and the effect sizes were all large in magnitude.

Figure 1 shows that the range of MWF across the control or the mTBI groups alone is large compared to the differences in means between the groups. This indicates that factors other than mTBI pathology contributed to MWF. Two candidate contributors are years of education and age; therefore the relationship between these factors and MWF across all controls and mTBI were evaluated using Pearson's correlations. Years of education was significantly positively correlated with MWF in all ROIs ($p < 0.044$) except in the left ILF ($p = 0.1$) but age was not significantly related to MWF in any ROI. Figure 3 shows MWF of global white matter in controls and mTBI plotted against years of education ($p = 0.002$ and $r = 0.54$) and age ($p = 0.3$ and $r = 0.2$). Correlations with GWM MWF for each subject group were also determined; control: education ($p = 0.049$, $r = 0.58$) and age ($p = 0.3$, $r = 0.33$); mTBI: education ($p = 0.09$, $r = 0.460$ and age ($p = 0.6$, $r = 0.150$).

In the ANCOVA, the group difference indicating trending toward lower GWM MWF in mTBI participants relative to controls ($p = 0.05$) after removing variances accounted for by years of education, which had a significant effect on the model ($p = 0.01$), and age, which did not p =

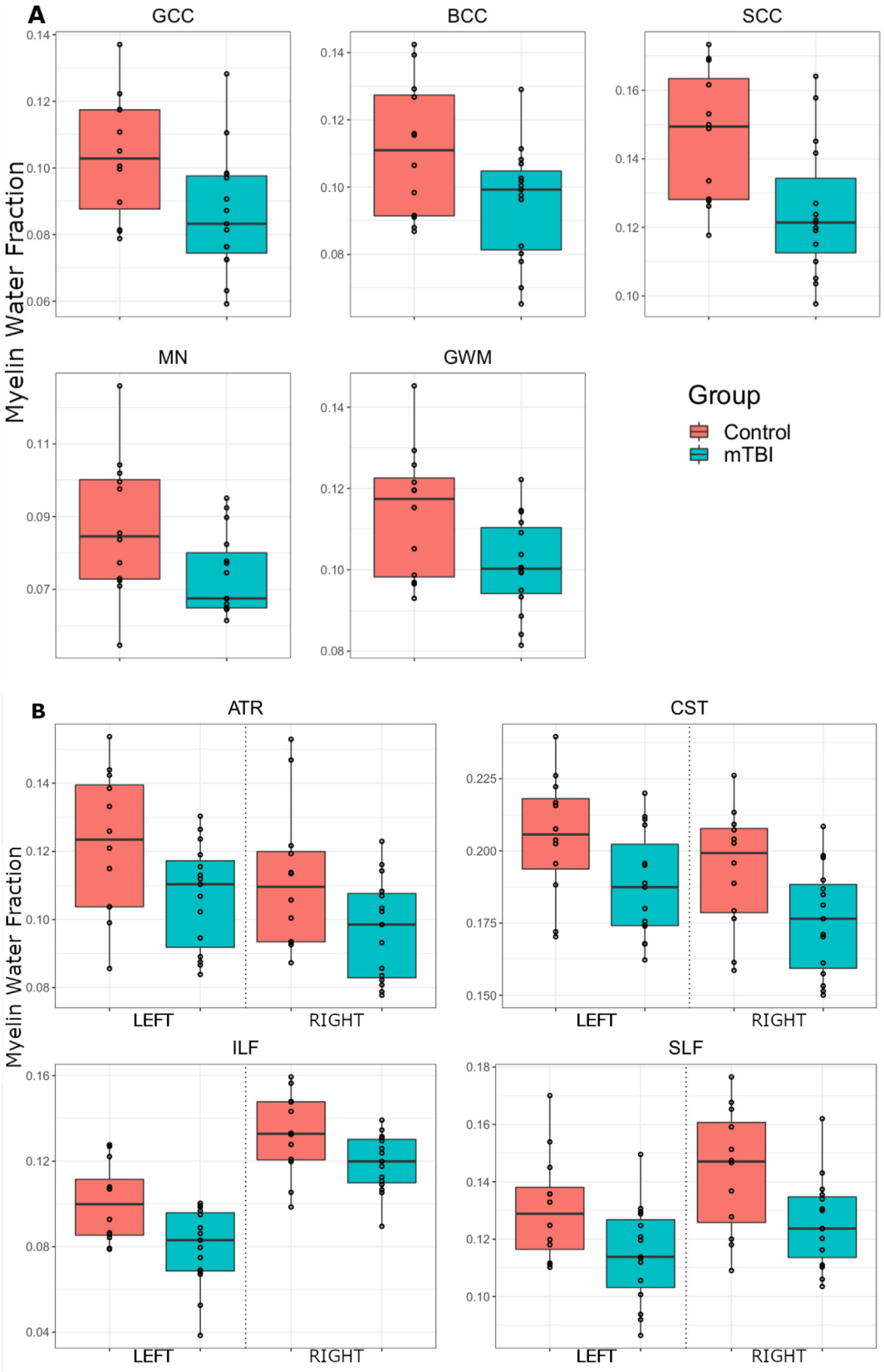

Figure 2. Myelin water fraction (MWF) for all controls and mild TBI subjects; in all regions of interest; A) genu of corpus callosum (GCC), body of corpus callosum (BCC), splenium of corpus callosum (SCC), minor forceps (MN), global white matter (GWM), B) left and right anterior thalamic radiation (ATR), superior and inferior longitudinal fasciculus (SLF and ILF respectively) and corticospinal tract (CST).

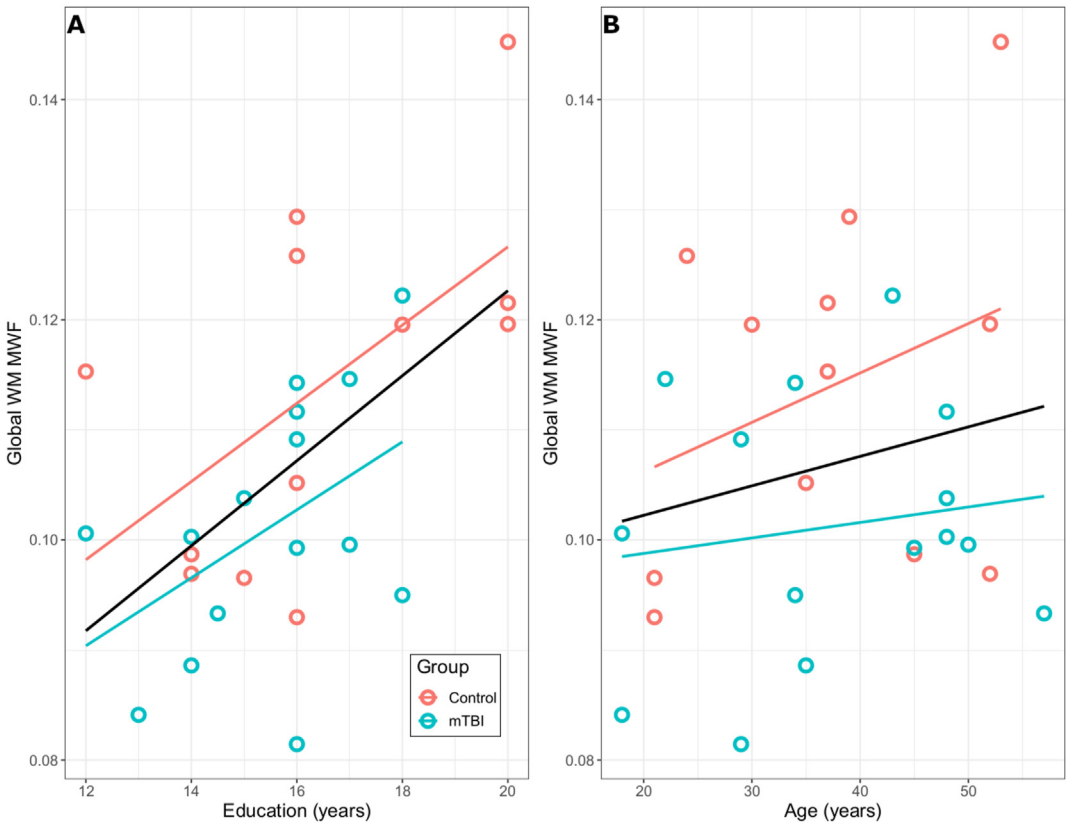

Figure 3. Effect of years of education and age on myelin water fraction (MWF) of global white matter (GWM) across controls and mild TBI. The linear fit over both control and mTBI is represented by the black line and the Pearson's correlation coefficient (r) and p-value between A) education (p=0.002, r=0.6) and B) age (p=0.3, r=0.2) with MWF.

0.6. After controlling for education and age, the following ROIs showed significant group differences: SCC ($p = 0.02$) ILFL ($p = 0.02$), and SLFR ($p = 0.04$), the other ROIs were not significant, $p > 0.05$.

3.3. Group differences in cognitive function and correlations between MWF and cognitive scores

Average age adjusted cognitive composite scores for Crystallized and Fluid cognition are summarized in Table 4 and the distribution of scores are presented in Figure 4 for each group. Fluid cognition was significantly higher in controls than mild TBI, although both means were above 100, which signifies average performance. Crystallized cognition was not statistically significantly different between groups and both means were above 115 which signifies a high average level of performance. Importantly, however, even though crystallized cognition was not statistically significantly different between groups (likely due to sample size), the Cohen's d indicated a large magnitude effect size for both Crystallized Fluid between-group comparisons. Figure 5 shows the scatterplots for the correlations between cognitive scores and GWM MWF for mTBI subjects. No significant correlations were found between mTBI MWF and cognitive scores in any ROI.

4. Discussion

In this study, we report several new findings in relation to MWF in a select group of individuals with chronic mTBI with persistent symptoms. First, we found significantly lower MWF in individuals with chronic mTBI compared with age, gender and education matched healthy individuals. Lower MWF was evident globally, and in all white matter regions examined . Global MWF was 12% lower, and MWF of the corpus callosum was 15–18% lower in the mTBI group. The number of years of education had a significant effect on most ROI MWF measures but age did not. After accounting for the variance in MWF associated with differences in years of education, GCC, left ILF, SCC, SLF and global white matter MWF still exhibited significant group differences between controls and mTBI, indicating that the reduced MWF in participants with chronic mTBI was not solely due to education. It is important to highlight that while the MWF findings may to some degree be related to the mTBI, there may also be a number of other factors, such as pre-existing differences between groups, ongoing symptoms, differences in psychological coping, differences in ability of the brain to repair itself, etc. that may reflect the decreases that we observed.

Previous recent studies on MWF in TBI have reported a range of findings. For example, Choi et al. [54] found significantly lower global

Table 4. Mean and sd of age-adjusted cognitive scores for controls and participants with mTBI (compared using an independent t-test and a Cohen's d to quantify effect size).

Subject Group	N	Crystallized Cognition Composite Score			Fluid Cognition Composite Score		
		Mean (sd)	p-value	Cohen's d	Mean (sd)	p-value	Cohen's d
Control	9	123(5)	$p = 0.06$	0.86	117(12)	$p = 0.02$	1.05
mTBI	15	115(11)			101(17)		

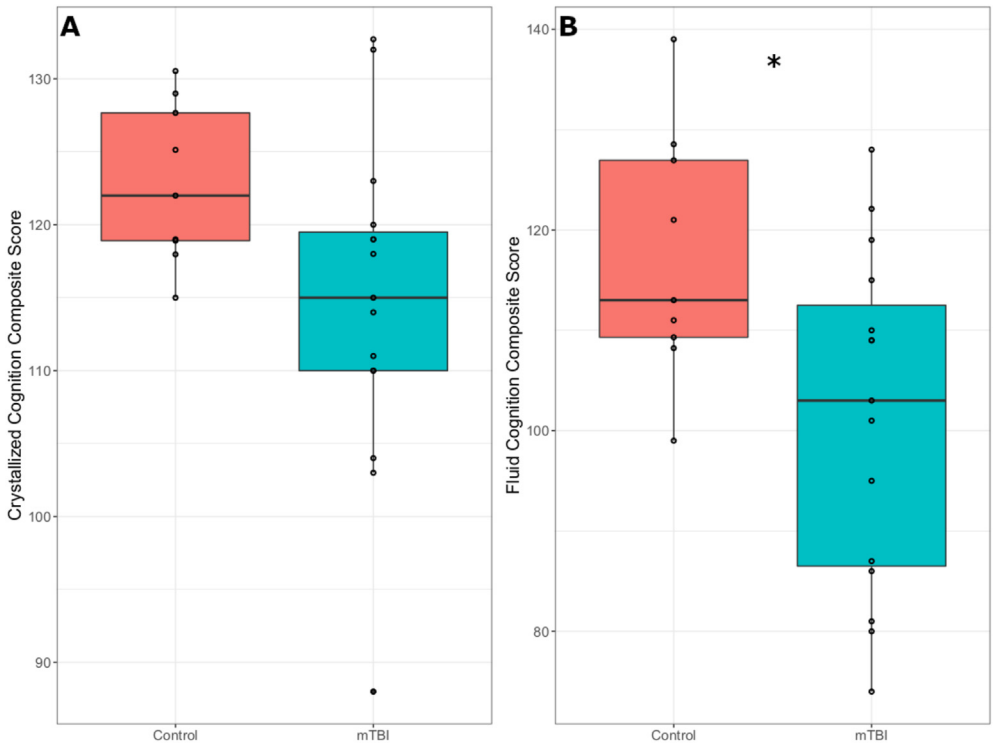

Figure 4. Age adjusted A) Crystallized and B) Fluid Cognitive Composite scores for each subject group and subject, and independent t-test comparison between control and mTBI. p-values are represented as *<0.05.

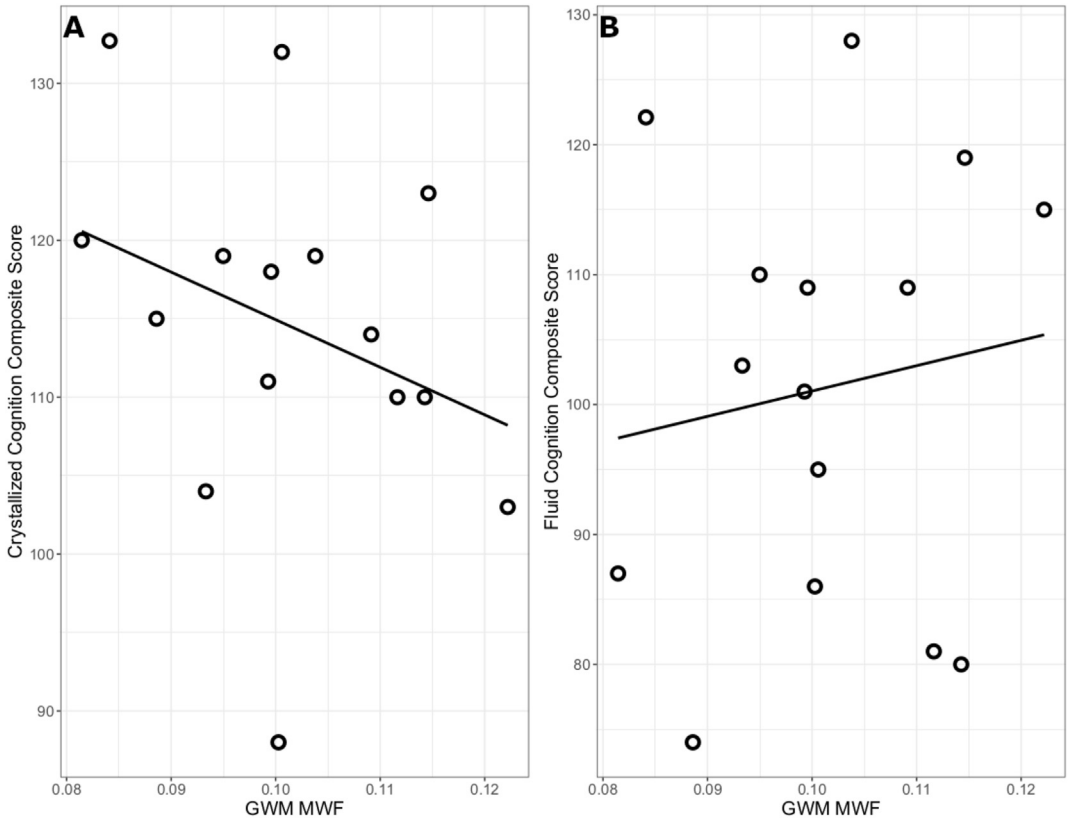

Figure 5. Age adjusted A) Crystallized (p=0.3, r=-0.3) and B) Fluid(p=0.6, r=0.1) Crystallized Composite scores compared to global white matter (GWM) myelin water fraction (MWF) for mild TBI participants.

apparent MWF in a TBI group compared to healthy controls; however, their participants with TBI had moderate-to-severe injuries and were only 3-months post-injury. A study [50] on athletes with concussion found a decrease in SCC MWF in the acute stage but return to baseline MWF at a month 2 follow up. In mice models [20], demyelination, remyelination, and excessive myelin are components of white matter degeneration and recovery in mild TBI with traumatic axonal injury. These studies suggest that in addition to the nature of the injury, myelin changes including increased myelin, reduced efficiency in clearing myelin debris combined with the immune response may have complex interactions that faciliatate ongoing neuroinflammation [20]. An ongoing neuroinflammatory response may in fact be associated with persistent symptoms. To our knowledge, this study is the first to report on changes in MWF in chronic mTBI and points to the need for further work to understand the complex underlying mechanisms of myelin change in individuals with persistent symptoms.

Of particular interest is that we found significantly lower mylelin water fraction in white matter tracts that have previously been implicated in mTBI [74]. These include specific regions of the corpus callosum, MN, right ATR, left ILF, SLF and CST. The corpus callosum is a bundle of long commissural fibres that connect the two hemispheres of the brain. Multiple studies and meta-analytic [74, 75] work show the CC is commonly affected (and thus examined) and the posterior portion of the CC (the splenium) is the area of the brain is more affected than the genu and body and is most consistently injured after TBI. As well, the splenium is an area known to be rich in myelin and thus has a high MWF [27]. We found the CC, and specifically the SCC may be sensitive to detecting differences between controls and mTBI.

MWF has been found to change as a function of age and years of education. Specifically, in humans, myelin development begins in utero and develops quickly through the first few years but continues to increase through adolescence and young adulthood [76, 77] and is thought to increase with learning and years of education in healthy adult brains [78, 79]. Our study add to the evidence of an association between MWF and years of education in healthy adults, however we also found this relationship in our TBI cohort. We did not find a significant correlation between age and MWF in either cohort or combined, which is different than what was found in the schizophrenia studies [53, 78]. This is most likely due to the much lower mean age in the schizophrenia study. MWF changes are more dramatic at lower ages and higher ages, while the increase of MWF with age is gradual in middle age [79], and thus the influence of age may not have been detectable in our cohort. These findings underline the importance of matching groups for years of education.

Individuals in the mTBI group showed lower Crystallized scores and especially Fluid cognitive scores than controls. Despite this, it should be noted that the mean cognitive scores were higher than or equal to 100 (average range) for both groups. Contrary to our hypothesis, we did not find a significant correlation between measures of MWF and either crystallized or fluid cognition for mTBI. A recent study reported a significant association between global MWF and processing speed, but this was evident in a sample of patients with moderate to severe TBI at 3 months post-injury [55]. Persistent cognitive deficits are rarely found in mTBI; however, here we found lower cognitive scores in mTBI than controls; however, we cannot rule out that the cognitive reductions in our patients were not due to prexisting cognitive differences between groups, highlighting that the results of this study may not be generalizable to all mTBI patients.

Traumatic brain injury imparts a major burden on society and even mild TBI can have long-term effects on some patients. There is increasing evidence that TBI is not a ‘single event’ but rather an ongoing process which unfolds across months, years, and possibly over a lifetime; thus, improved monitoring of long-term effects of TBI is essential [80]. White matter tracts are particularly vulnerable to a TBI and monitoring the myelination of these tracts may expand our knowledge and inform the development of diagnostic and prognostic biomarkers. Myelin water fraction is a powerful quantitative technique to examine myelin content and has been used to examine a variety of brain diseases and disorders [38]. Here we show MWF differences in mTBI up to 6 months post-injury, compared to healthy controls, and show the utility of MWF to examine long-term bran changes in patients with mild TBI. Further study is needed to identify the mechanisms underlying the lack of myelin regeneration and strategies to enhance the recovery process in individuals with chronic mTBI with persistent symptoms.

Declarations

Author contribution statement

Bretta Russell-Schulz: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Irene M. Vavasour, Jing Zhang, Victoria Purcell, Angela M. Muller, Leyla R. Brucar: Performed the experiments; Analyzed and interpreted the data.

Alex L. MacKay: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Ivan J. Torres, William J Panenka, Naznin Virji-Babul: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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