

An Analysis of Concussions and Cortical Structures

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Introduction

Every year about 300,000 sport-related concussions occur in the United States.¹ A concussion is defined as a blunt force to the head, neck, or body that sends a sudden force to the brain and results in symptoms,² but does not meet the criteria for a more severe injury (e.g., no skull fracture, no brain bleed). Participation in contact and collision sports (e.g., American football, hockey) represents a risk factor for sport-related concussion, which are sustained more often by collegiate athletes than high-school athletes, although high-school states sustain more concussions proportional to other injuries.¹ However, a hesitancy to disclose symptoms, an issue for both high school and collegiate athletes, means that the true prevalence of these insidious injuries is likely underestimated. For example, nearly one-third of former collegiate athletes admitted to not disclosing sport-related concussion symptoms for numerous reasons (e.g., peer pressure, indifference, and lack of concussion awareness).³ There is no biomarker of a concussive brain injury or recovery from that injury, a striking gap in medical knowledge given that one of the greatest risk factors for a concussion is a history of past concussion. Instead, clinical decision making depends exclusively on signs and symptoms.

Despite being described as ‘functional’ injuries, structural magnetic resonance imaging (sMRI) has been widely employed as a tool to study the effects of concussion on brain morphology, often defined by cortical thickness and subcortical brain volumes. Changes after concussion are both diffuse (e.g., reduced white and grey matter volumes) and focal.⁴ Two independent, cross-sectional studies, each recruiting 20-30 male athletes with a diagnosed concussion, reported cortical thinning in frontal and temporal areas acutely—within 3 months of injury⁴—and chronically, many months later.⁵ However, other studies suggest these effects

require more distant longitudinal measurements for context. For example, a study of 49 patients, 25% of whom sustained sport-related concussions, exhibited increasing frontal cortex thickness from 1 week to 1-year post-injury compared to age- and sex-matched controls. Moreover, the effect was greatest in patients who exhibited the worst concussion outcomes.⁶ On the other hand, differences in brain morphology have also been observed between athletes competing in sports that carry a high risk of concussion and those that carry a low risk of concussion. Mills et al.⁷ observed cortical thinning in frontal and temporal areas in control (volleyball) athletes over 4 years, but not in football athletes, only 30% of whom reported a history of concussion. This suggests that exposure to subconcussive impacts—even in the absence of a diagnosis—might affect trajectories of brain development.⁷ Moreover, it highlights the need for careful selection of control groups. Ultimately, these studies have (i) relied on mostly smaller samples, (ii) only considered one aspect of cortical morphology (i.e., thickness or volume), and (iii) only considered macrostructural, morphometric features, potentially explaining the inconclusive findings.^{8,9,10}

Beyond morphometry, myelination is a cortical architectonic feature with a distinct and evolutionarily conserved spatial gradient.¹¹ Other studies of post-concussion myelin have focused on long-range white matter fibers, but have mostly ignored the potential effects on intracortical myelination.¹² One study demonstrated long-term changes in T1-weighted tissue intensities along the grey-white matter boundary (i.e., the inner border of the cortical ribbon) that the authors interpreted to represent myelin remodeling.¹³ Mahoney et al.¹⁴ more directly inferred cortical myelin from the T1w/T2w ratio, revealing the greatest reductions in myelin six months post-concussion compared to controls. The participants of the study were only sampled seven days post-concussion and six months later. Within the time between the occurrence of a

concussion and seven days, there is an unknown acute phase of recovery. Similarly, a different study used the same metric to reveal lower cortical myelin content following a lifetime of concussion exposure among U.S. military veterans.¹⁵ These findings suggest that intracortical myelin may be a biomarker of the long-term effects of concussion, but how soon after injury these changes occur remains poorly understood. Therefore, we sought to test for differences in cortical myelination between athletes with and without a diagnosed concussion, 24-48 hours after injury and 8 days later. We hypothesized that athletes with a concussion would demonstrate reduced intracortical myelin and the effects would be greatest 8 days after injury.

Methods

Participants

This was a secondary analysis of data from the ‘Head-to-Head II’ project that enrolled high school and collegiate athletes from Southeastern Wisconsin.¹⁶ Data were retrieved from FITBIR. The current analysis focused on 121 participants with imaging data 24-48 hours after a diagnosed concussion and 8 days later.

MRI Acquisition & Processing

This analysis focused on anatomical scans performed on a 3 Tesla GE MR750<>. T1-weighted (T1w) images were acquired using an MPRAGE protocol (160 slices, 1.0 mm thickness, 256 x 256 matrix, TR/TE = 3.008/7.592 ms). T2-weighted (T2w) images were collected using a CUBE sequence (160 slices, 1.0 mm thickness, 256 x 256 matrix, TR/TE = 64.2/2500 ms). Anatomical MRI data (T1w and T2w scans) were downloaded from FITBIR and processed using Human Connectome Project *FreeSurferPipeline*¹⁷ implemented in QuNex.¹⁸

Statistics

We took two complementary approaches based on prior findings to test for group differences in cortical myelination 24-48 hours after the concussion. First, we performed t-tests

to compare T1w/T2w ratio at each or 360 regions-of-interest between participants with a concussion and (i) controls playing the same sport and (ii) controls playing a different sport with a low risk of concussion. Second, we considered concussion history by testing group differences using simple linear regression models while controlling for a history of concussion (binary; positive vs. negative). Finally, we repeated these steps to test for differences 8 days after concussion, given that differences in cortical myelin may represent prolonged and dynamic injury or repair processes.

Table 1. Demographics

	Case	In-sport	Out-sport	Total
Sample (Acute/Day8)	43/43	48/43	30/34	121/120
Age (SD) years	18.6 (1.7)	20 (1.7)	19 (1.8)	18.9 (1.7)
History of Concussion	47%	39%	0%	31%

Results

The most parsimonious approach did not yield differences in myelin between the groups; athletes who had sustained a concussion did not exhibit differences in cortical myelin 24-48 hours later compared to in-sport or out-of-sport controls. While controlling for sport-related concussion history, we also observed no difference between groups. However, when examining group differences at Day 8, we observed 24 brain areas that exhibited greater cortical myelin content in those with concussion relative to out-of-sport controls, while controlling for a history of sport concussion. The differences were greatest in the frontal and temporal lobe (Fig. 1). On the other hand, there were more diffuse reductions in cortical myelin observed in those with a history of concussion compared to those without a history of concussion. These were greatest in sensorimotor areas (e.g., post central gyrus, visual cortex; Fig. 2).

Figure 1

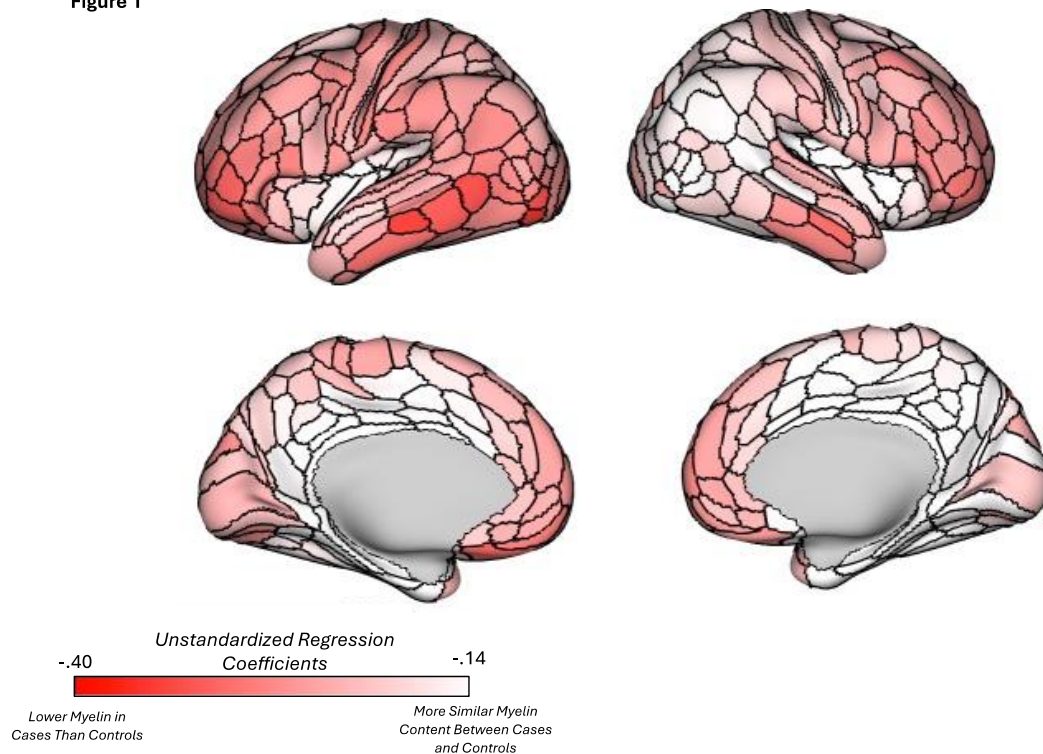


Figure 1. Myelin in the cases and out of sport controls. Less myelin in case is depicted in dark red. Similar levels of myelin in both cases and controls is depicted in light red or white.

Figure 2

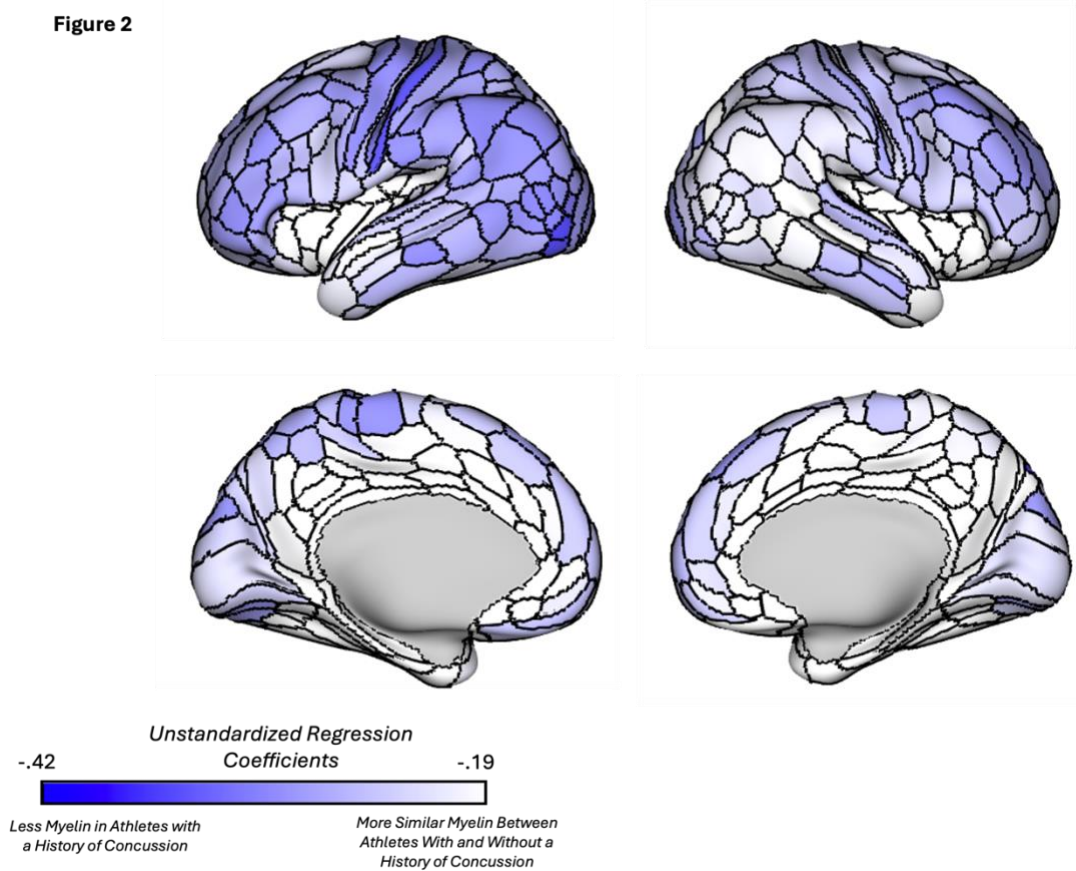


Figure 2. Differences in myelin between athletes with a history of concussion or not among cases and out-of-sport controls. Less myelin for athletes with a history of concussion is depicted in a dark blue. Similar myelin for athletes with and without a history of concussion is depicted in a lighter blue or white.

Discussion

The goal of this secondary analysis was to test for the effects of sport-related concussion on cortical myeloarchitecture—as defined by the T1w/T2w ratio—within the first week of recovery. Prior studies suggest that individuals with a history of concussion exhibit less myelin^{14,15} relative to those without, but these studies do not tell us how soon after the injury differences began. We observed two novel and interesting patterns. First, football players who had sustained a concussion exhibited greater myelin content than out-of-sport controls 8 days after diagnosis. Interestingly, these differences were observed in the frontal and temporal lobes, where population-level studies have shown there to be lesser myelin content.¹⁷ Higher T1w/T2w

may represent greater iron deposition, which was recently found to be associated with headache symptoms after concussion.¹⁹ Iron accumulation is a putative biomarker for concussion suggests pathophysiological changes occurring in the brain. Given the role of these areas in regulating attention and learning, these reports may suggest a mechanism through which concussion delays a 'return-to-learn'.

Second, only when comparing cases and out-of-sport controls did we observe that athletes with a history of concussion have lesser myelin content than those without a history of concussion in the parietal and occipital lobes. This pattern is similar to a study of veterans with a history of TBI.¹⁵ The lower intracortical myelin content could also explain apparent cortical atrophy reported by others,²⁰ as the grey-white boundary would be modeled closer to the pial surface.

There are as yet no therapies capable of recovering or boosting myelin in humans, but promising evidence from preclinical models all shown evidence of contributing to remyelination with animal models.²¹ Taib et al. suggest sensorimotor deficits and delays in cognitive flexibility occur 3 days up to 1 month or longer post-injury,²² yet the patterns we observed suggest that physiological recovery of these circuits may be much longer. Possible causes of cross-sectional enlargement are (acute or chronic) neuroinflammation and compensatory hypertrophy. Brain injuries cause increased activity and enlargement due to edema. Ross et al. indicate cross-sectional enlargement occurs a week to 3 months after injury.²³ Different brain areas atrophy and enlarge during recovery (day 8), showing heavy myelination on the T1w/T2w ratio.

Our study is not without limitations. First, we only analyzed data from male athletes. We also did not consider symptom severity or the number of concussions sustained by those with a history. Future studies should consider comparing cortical myeloarchitecture in male and female

athletes after concussion. In conclusion, we found increased intracortical myelin in athletes 8 days post-injury. These findings emphasize the need for further research to determine why there was an opposite effect on history. It also encourages researchers to find a way to boost myelination in athletes in recovery.

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