Neuroscience Letters 650 (2017) 52–59

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

# Concussion induces focal and widespread neuromorphological changes

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## HIGHLIGHTS

- Single concussion associated with reduced white, grey matter and total cortical volume.
- Cortical thinning, primarily in left frontal areas, also observed.
- No differences were observed in the cerebellum or subcortical structures.
- A single concussion induces measurable changes in brain structure.
- Changes manifest as diffuse and local patterns of altered neuromorphometry.

## ARTICLE INFO

*Article history:*
Received 27 January 2017
Received in revised form 31 March 2017
Accepted 14 April 2017
Available online 17 April 2017

*Keywords:*
Concussion
MRI
Cortical thickness
Cortical volume
Cerebellum

## ABSTRACT

Concussion induces transient, and oftentimes chronic, lingering impairment to mental functioning, which must be driven by some underlying neurobiological perturbation – however, the physical changes related to sequelae are difficult to detect. Previous imaging studies on concussion have focused on alterations to cortical anatomy, but few have examined the cerebrum, subcortex, and cerebellum. Here, we present an analysis of these structures in a single cohort (all males, 21 patients, 22 controls) using MRI and diagnosed with a single-concussive episode in the acute and sub-acute stages of injury. Structural images were segmented into 78 cortical brain regions and 81,924 vertices using the CIVET algorithm. Subcortical volumetric analyses of the cerebellum, thalamus, globus pallidus, caudate and putamen were conducted following segmentation. Participants with concussion were found to have reduced white and grey matter volume, total cortical volume, as well as cortical thinning, primarily in left frontal areas. No differences were observed in the cerebellum or subcortical structures. In conclusion, just a single concussive episode induces measurable changes in brain structure manifesting as diffuse and local patterns of altered neuromorphometry.



## 1. Introduction

Concussion is the most common type of acquired brain injury, and even minor injuries can lead to short- and long-term structural and functional changes in the brain that are measurable via non-invasive neuroimaging [1], even in those who are asymptomatic [2]. Concussion is defined as the instantaneous and transient impairment to mental functioning [3] (although chronic symptoms can occur); patients present less severe deficits, in relation to more severe traumatic brain injury (TBI), that include mild or short-

*Abbreviations:* CLASP, Constrained Laplacian Anatomical Segmentation using Proximities; CT, Cortical thickness; DAI, Diffuse axonal injury; GM, Grey matter; MAGeT, Multiple Automatically Generated Templates; MNI ICBM152, Montreal Neurological Institute International Consortium for Brain Mapping 152; MRI, Magnetic resonance imaging; TBI, Traumatic brain injury; WASI, Wechsler Abbreviated Scale of Intelligence; WM, White matter.

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http://dx.doi.org/10.1016/j.neulet.2017.04.026

lasting alterations to conscious awareness, dizziness, nausea, and headaches [4,5]. Additional cognitive complaints are not uncommon and can include irritability, fatigue, inattention, impulsivity, and memory deficits – the persistence of such lingering symptoms is known as post-concussive syndrome (PCS), and can affect up to 20% of patients [6]. Furthermore, long-term psychopathology, such as anxiety and depression [7] are often reported in those with PCS.

At the neuroanatomical level, concussion is thought to impart diffuse (as opposed to *focal*) injury [8], and wide-area/global and microstructural/local disturbances to tissue [9], including axonal stretching and cell body damage, along with a cascade of biochemical changes that perturb normative neuronal function [10]. Such neuropathology is aetiological in regards to cognitive complains [11]. Structural neuroimaging studies in humans using MRI have probed grey matter (GM) volume, and revealed atrophy in patients in the early (subacute) and later stages (chronic) post-injury [12], and across a range of traumatic brain injury (TBI) severities [13]. However, the effect of concussion on cerebellar and sub-cortical structures is relatively unknown, and a comprehensive picture of brain morphological changes is important to improve our understanding and repercussions of concussive injury.

Here we characterise structural cerebral, cerebellar and subcortical brain changes in the acute and subacute stages (less than 3 months post-injury) of a single concussive episode. We used structural MRI to examine neuroanatomical alterations in a group with injury compared to a healthy matched control group. We tested the hypothesis that concussion induces changes of cortical and subcortical structures, and predicted differential cortical volume and thickness patterns between groups, as well as subcortical and cerebellar effects.

## 2. Materials and methods

### 2.1. Participants

Forty-three young adult male participants were recruited to this study: 21 participants had a concussion (mean age ± standard deviation = 31.2 ±6.8 years; range 21–44 years), while the remaining 22 participants without concussion served as controls (mean age ± standard deviation = 27.1 ±4.9 years; range 20–39 years). This cohort represents a subset of the participants reported in other studies from this laboratory [14–16].

Participants with concussion were recruited from a level I trauma center (Sunnybrook Health Sciences Centre) in Toronto. Inclusion criteria for the concussion group included an age range between 20 and 45 years, a concussion within the previous 3 months (mean time since injury at scan = 33.33 days), no reported prior history of concussion and a normal head computed tomography scan at admission. Symptomatology was not a prerequisite for inclusion, but when present was limited to loss of consciousness of no more than 30 min, post-traumatic amnesia, alterations of consciousness, and/or confusion of no more than 24 h, and Glasgow Coma Scale (GCS) greater than 13 in the first 24 h after injury [17]. Given that the principal aim of this study was examine whether a single injury induce measurable changes in morphometry, symptomatology was not part of our inclusion criteria.

Control individuals were recruited from the local community and through flyers posted at the hospital, and were excluded if they had a self-reported history of neurological, psychological and psychiatric disorders, as well as a previous concussive head injury that resulted in a transient alteration of mental function. Exclusion criteria for both groups included taking anti-convulsant medications, benzodiazepines and GABA antagonists, if they presented with any contraindication to MRI, or if they had gross neurostructural abnormalities and/or significant artefacts in their MRI scan which prevented their images from being analysed.

This study was approved by and conducted in accordance with the Research Ethics Boards of The Hospital for Sick Children and Sunnybrook Health Sciences Centre. Informed written consent was obtained from all participants.

#### 2.1.1. Cognitive-behavioural assessment

The Wechsler Abbreviated Scale of Intelligence (WASI) [18] was used to ensure the groups were matched on intelligence, and the Sports Concussion Assessment Tool 2 (SCAT2) [19] was administered to assess symptomatology (absolute number of symptoms displayed, plus severity which is the number of symptoms times rating on an individual scale). All Control and Concussion group participants were assessed on the same day as the scanning session.

### 2.2. MRI acquisition

All participants underwent a structural brain scan, using a 3T Siemens Trio MRI scanner (MAGNETOM Tim Trio, Siemens AG, Erlangen, Germany) having a 12-channel head coil at the Hospital for Sick Children, Toronto. The sequence that was used was a T1-weighted 3D sagittal magnetization-prepared rapid gradient echo (MPRAGE) with TR = 2300 ms, TE = 2.96 ms, TI = 900 ms, and FA = 9°. A FOV of 240 × 256 mm with 192 slices yielded 1 mm isotropic voxels. Motion restriction and stabilization of the head during imaging was attained with foam padding.

#### 2.2.1. Image processing

*2.2.1.1. Cortical analyses.* The MRIs were first linearly registered into a common 3-dimensional space, using the corticometric iterative vertex based estimation of thickness (CIVET) pipeline [20]. This algorithm corrected for RF inhomogeneity artefacts [20,21], and categorized cortical regions into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) [20]. This categorization was carried out in two steps, the first of which created discrete tag points, and the second, which computed the partial volume information for each of the tissue categories [22]. The Constrained Laplacian Anatomical Segmentation using Proximities (CLASP) method [22] was used to produce the grey and white matter surfaces. These surfaces were utilized in computing the cortical surface area (SA). The surface boundary identification was consequently improved upon through expansion of the white matter surfaces until they reached the pial surface [22]. This yielded 4 surfaces (2 per hemisphere) each with 40,962 vertices, which were registered to the MNI ICBM152 surface template, and facilitated a group-wise comparison. The distance between surface boundaries was used in calculating the cortical thickness. Cortical thickness was then analysed with a lobe-based approach, using the 78 brain regions, as segmented using the Automated Anatomical Labelling (AAL; Fig. 1) atlas [23], as well as with a vertex-based analysis of all 81,924 vertices. A surfaced-based blurring kernel of 20 mm was used. Cortical thickness, together with surface area (SA), was used in computing the cortical volume [24,25].

*2.2.1.2. Analyses of the cerebellum, thalamus and basal ganglia.* Segmentation of the cerebellum and basal ganglia (Fig. 1) was conducted on the MR images using the Multiple Automatically Generated Templates (MAGeT) algorithm [26,27]. In this algorithm, manually segmented images are used as atlases. Five atlases were available for the cerebellum [28], and one atlas for the basal ganglia [29]. An arbitrary subset of the participants' MR images were designated as "templates". They were pair-wise registered to each of the atlases, creating multiple anatomical segmentations, thereby producing a template library of labeled atlases per structure. A procedure called "voxel voting" was then completed, in which

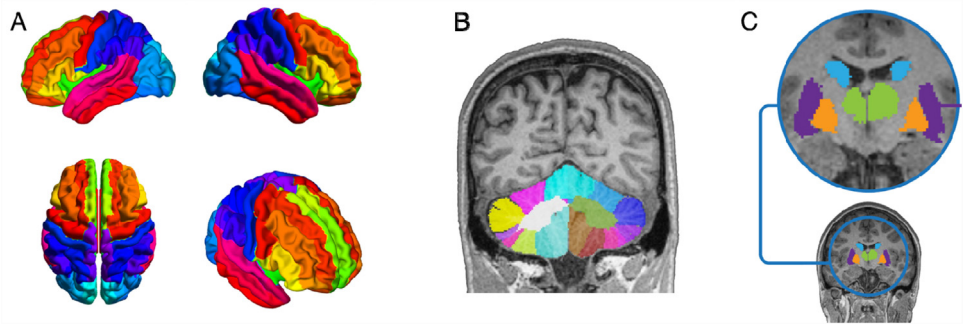


**Fig. 1.** Parcellation for the (A) Anatomical Labelling Atlas, (B) cerebellar and (C) basal ganglia segmentation.

**Table 1**
Patient demographics and clinical data for the Concussion group.

| ID | Age | WASI | SCAT2 Symptoms | SCAT2 Severity | Days since injury until MRI | LOC | GCS | PTA | Mechanism |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 32 | 85 | 15 | 36 | 9 | no | 14 | no | Sports |
| 2 | 41 | 94 | 0 | 0 | 27 | altered | 14 | <24 h | Sports |
| 3 | 22 | 120 | 2 | 9 | 30 | yes | 14 | <24 h | MVC |
| 4 | 27 | 107 | 5 | 8 | 47 | yes | 15 | no | Pedestrian/Car |
| 5 | 21 | 101 | 7 | 9 | 38 | no | 15 | no | MVC |
| 6 | 35 | 101 | 6 | 18 | 49 | no | 15 | no | MVC |
| 7 | 26 | 105 | 5 | 8 | 22 | yes, 30 s | 14 | yes | Sports |
| 8 | 22 | 101 | 1 | 1 | 51 | yes | 15 | no | Fall |
| 9 | 32 | 126 | 4 | 6 | 53 | altered | 14 | no | Sports |
| 10 | 40 | 102 | 13 | 27 | 62 | yes, 2 min | 13-14 | yes | Fall |
| 11 | 38 | 106 | 22 | 75 | 45 | yes, brief | 15 | no | MVC |
| 12 | 44 | 106 | 5 | 6 | 34 | yes, brief | 14 | <24 | Fall |
| 13 | 37 | 121 | 8 | 18 | 26 | yes, 2 min | 15 | no | MVC |
| 14 | 35 | 120 | 20 | 74 | 10 | yes, 5 min | 14 | <20 min | MVC |
| 15 | 28 | 118 | 9 | 12 | 7 | yes, 2 min | 15 | yes, ~24 h | Sports |
| 16 | 33 | 91 | 13 | 35 | 60 | unknown | 15 | no | Fall |
| 17 | 25 | 131 | 12 | 27 | 35 | no | 15 | yes | Work accident |
| 18 | 30 | 90 | 10 | 16 | 11 | altered | 14 | no | Accident |
| 19 | 36 | 125 | 15 | 24 | 10 | yes, 2 min | 14 | no | Sports |
| 20 | 22 | 134 | 9 | 12 | 37 | no | Missing | no | Sports |
| 21 | 30 | 115 | 18 | 38 | 37 | no | Missing | no | Sports |
| *mean* | 31.24 | 109.48 | 9.48 | 21.86 | 33.33 | | | | |
| *std* | 6.81 | 14.00 | 6.17 | 20.76 | 17.26 | | | | |

WASI, Weschler's Abbreviated Scale of Intelligence; SCAT2, Sports Concussion Assessment Tool 2; LOC, Loss of consciousness; GCS, Glasgow Coma Scale; PTA, Post-traumatic Amnesia.

these atlases were averaged and the most frequently occurring segmentation label per voxel was selected [30]. This yielded a more accurate final anatomical segmentation. Automatic segmentation of the cerebellum and basal ganglia structures provided volumetric information for individual participants, which was used for group-wise comparisons. Structural volumes were also divided by total cerebrum volume (computed by the sum of the grey matter, white matter and cerebrospinal fluid volumes in CIVET) to provide the relative volume of each structure.

This automatic segmentation not only identified the gross anatomical structures, but also the sub-structures within them. In the case of the cerebellum: 13 sub-fields were segmented: lobule 1–2, lobule 3, lobule 4, lobule 5, lobule 6, Crus 1, Crus 2, lobule 7b, lobule 8a, lobule 8b, lobule 9, lobule 10, white matter. In the basal ganglia and surrounding region, 4 structures were segmented: the thalamus, globus pallidus, caudate, and putamen. Corresponding sub-fields in the right and left hemisphere were combined, and the total volumes were compared between groups.

### 2.3. Statistical analysis

The dependence of total brain volume, GM volume, WM volume, cortical thickness, SA, cortical volume, cerebellar and subcortical volumes on Group and Age was tested using an Analysis of Variance (ANOVA). When multiple comparisons were conducted on a single data set, we accounted for it using the False Discovery Rate (FDR) technique [31]. The FDR was also applied to the vertex-based cortical thickness analysis. FDR values less than 5% were considered significant, and the respective values are provided for each significant result. Data values are quoted in the form of mean ± standard deviation. Error bars in bar-graphs and shaded regions in regression fits show the 95% confidence interval (CI).

## 3. Results

### 3.1. Patient demographics and cognitive-behavioural assessment

Patient demographics and cognitive-behavioural assessment scores for the Concussion group are shown in Table 1. Intelligence Quotient, as measured through the WASI test, was not significantly different between groups.

### 3.2. Cerebral parameters

White matter (WM) volume, mean cortical thickness, and total cortical volume were found to be significantly smaller in the Concussion group compared with controls. Neither total brain volume nor grey matter volume differed between the groups (Table 2). All cerebral parameter contrast test-statistics were found to be independent of symptom severity.

**Table 2**
Cerebral Parameters, showing mean and ±1 standard deviation. Bold indicates a significant group difference.

| | Concussion | Control | P (F) values Group Effect | P (F) values Group:Age Effect | P (F) values SCAT Severity Effect |
|---|---|---|---|---|---|
| n | 21 | 22 | | | |
| Total Brain Volume [$10^5$ mm$^3$] | 30.84 ± 2.15 | 31.58 ± 2.46 | 0.3119 (1.0495) | 0.4793 (0.5101) | 0.6846 (0.1675) |
| White Matter Volume [$10^5$ mm$^3$] | 13.58 ± 1.45 | 13.39 ± 1.18 | 0.6440 (0.2169) | 0.8409 (0.0408) | 0.2668 |
| Grey Matter Volume [$10^5$ mm$^3$] | **10.05 ± 0.83** | **10.62 ± 0.83** | **0.03288 (4.8936)** | **0.75325** | 0.35653 (0.8712) |
| Total Surface Area [$10^5$ mm$^2$] | 1.93 ± 0.10 | 1.98 ± 0.13 | 0.1573 (2.0794) | 0.3249 (0.9942) | 0.58204 |
| Mean Cortical Thickness [mm] | 3.26 ± 0.13 | 3.33 ± 0.12 | 0.06457 (2.6178) | 0.99637 (0.0000) | 0.71804 |
| Total Cortical Volume [$10^5$ mm$^3$] | **5.12 ± 0.38** | **5.42 ± 0.46** | **0.02558 (5.3892)** | **0.53183 (0.3980)** | 0.44709 |

**Table 3**
A lobe-based analysis of mean cortical thickness (in mm, with ±1 standard deviation), showing regions exhibiting signification group differences.

| Cortical Region | Brodmann Area | Concussion | Control | Group Effect F value | Group Effect Uncorrected P value | Group Effect Corrected P value (Q) | Severity Effect Corrected P value (Q) |
|---|---|---|---|---|---|---|---|
| Left Precentral gyrus | 1 | 2.92 ± 0.17 | 3.08 ± 0.16 | 11.9035 | 0.00136 | 0.0436 | 0.3830 |
| Left Middle frontal gyrus | 7 | 3.06 ± 0.16 | 3.23 ± 0.15 | 11.3978 | 0.00168 | 0.0436 | 0.6205 |
| Right Parahippocampal gyrus | 38 | 3.46 ± 0.17 | 3.70 ± 0.19 | 17.4847 | 0.00016 | 0.0124 | 0.9788 |

**Table 4**
Relative volume (%) for subcortical structures with ±1 standard deviation.

| | Concussion | | Control | |
|---|---|---|---|---|
| Hippocampus | 0.16 | ±0.020 | 0.16 | ±0.013 |
| Cerebellum | 4.14 | ±0.37 | 4.03 | ±0.30 |
| Thalamus | 0.02 | ±0.0022017 | 0.02 | ±0.0021 |
| Globus Pallidus | 0.01 | ±0.0009341579 | 0.01 | ±0.00056 |
| Caudate | 0.25 | ±0.02878929 | 0.25 | ±0.018 |
| Putamen | 0.33 | ±0.02601264 | 0.33 | ±0.021 |

A lobe-based analysis of cortical thickness showed a group effect – but no age or symptom severity effect – in several regions, primarily in the left frontal lobe. In all cases, Concussion participants had reduced cortical thickness in the affected area compared with Control participants. A complete list of affected regions is included in Table 3. Surface area did not differ between groups independently of brain region (Table 4).

The vertex-based cortical thickness analysis provided information about local differences that were otherwise averaged out in the lobe-based analysis. Localized thinning for the Concussion group was found in the left superior frontal gyrus, left postcentral gyrus, and right parahippocampal gyrus, while localized thickening was found in the right superior temporal gyrus. These are highlighted in the t-statistics maps and accompanying bar-graphs in Fig. 2.

### 3.3. Sub-cortical and cerebellar volumes

No group effect was observed for any other basal ganglia structure or the thalamus, or any cerebellar regions measured (Fig. 3).

## 4. Discussion

### 4.1. Summary

A number of findings emerged from this study: First, we observed reductions in WM volume, mean cortical thickness and total cortical volume following a single concussion that were independent of age or intelligence. Second, cortical thinning was observed in the left superior frontal gyrus, postcentral gyrus, and the right parahippocampal gyrus – a fourth area, in the right superior temporal gyrus, displayed a more focal increase in cortical thickness. Finally, there were no significant differences in any subcortical structures or lobules of the cerebellum.

### 4.2. Reduced WM volume in concussion

Reductions in WM volume may hinge on tract disruption due to stretching, inflammation, crushing and separation from GM, promoting deafferentation and demyelination of axons – such a view is supported by diffusion tensor imaging (DTI) studies that have revealed atypical corpus callosum metrics that are related to the magnitude of an impact [32]. Pertinent to the manifestation of sequelae, it has also been shown that WM fractional anisotropy (FA) changes [33] are intrinsically linked to regional GM activation patterns, and such cortical dysfunction could explain cognitive symptoms. Other evidence shows that mild diffuse axonal injury (DAI) disrupts structural connections [34] that link multiple brain regions and thus support interregional communication – a critical mechanism in the spatiotemporal orchestration of cortical processes. The phenotype of these disturbances is cognitive dysfunction [15,35,36].

### 4.3. Reduced cortical thickness and volume in concussion

We found that global measures of brain morphology (cortical thickness and volume) were reduced following a single concussion, as well as focal areas of the cortex. Animal studies point to rapid alterations in GM structure post-injury, with abrupt, transient local thickening, and subsequent thinning [37]. This is due to both WM disruption and a cascade of neurochemical events. WM disruption, in the form of axonal shearing (axotomy), can induce Wallerian degeneration [38,39] and concomitant reactive astrocytosis that would contribute to GM atrophy [40]. Moreover, the "neurometabolic cascade of concussion" [41] would also explain thickness and volume reductions observed here. Such biochemical events impair neurotransmission, driven by an excessive release of excitatory neurotransmitters that evoke hyper-excitation and activation [41], creating a cell membrane ionic imbalance that is excitotoxic [42]. It is known that cortical thickness (and by extension, cortical volume) is directly related to the number, density, and size of neurons [43,44] – thus, comparative reductions in both measures would support the interpretation that concussion has resulted in apoptosis, atrophy and a decrease in neuronal number [45].

A lobe-based analysis revealed that reduced cortical thickness was primarily located in the left frontal regions. This area plays a role in executive function, including working memory [46], mental flexibility [47], attention [48] and inhibition [49], facets of cognition that have been shown to be perturbed by concussion [15,50].

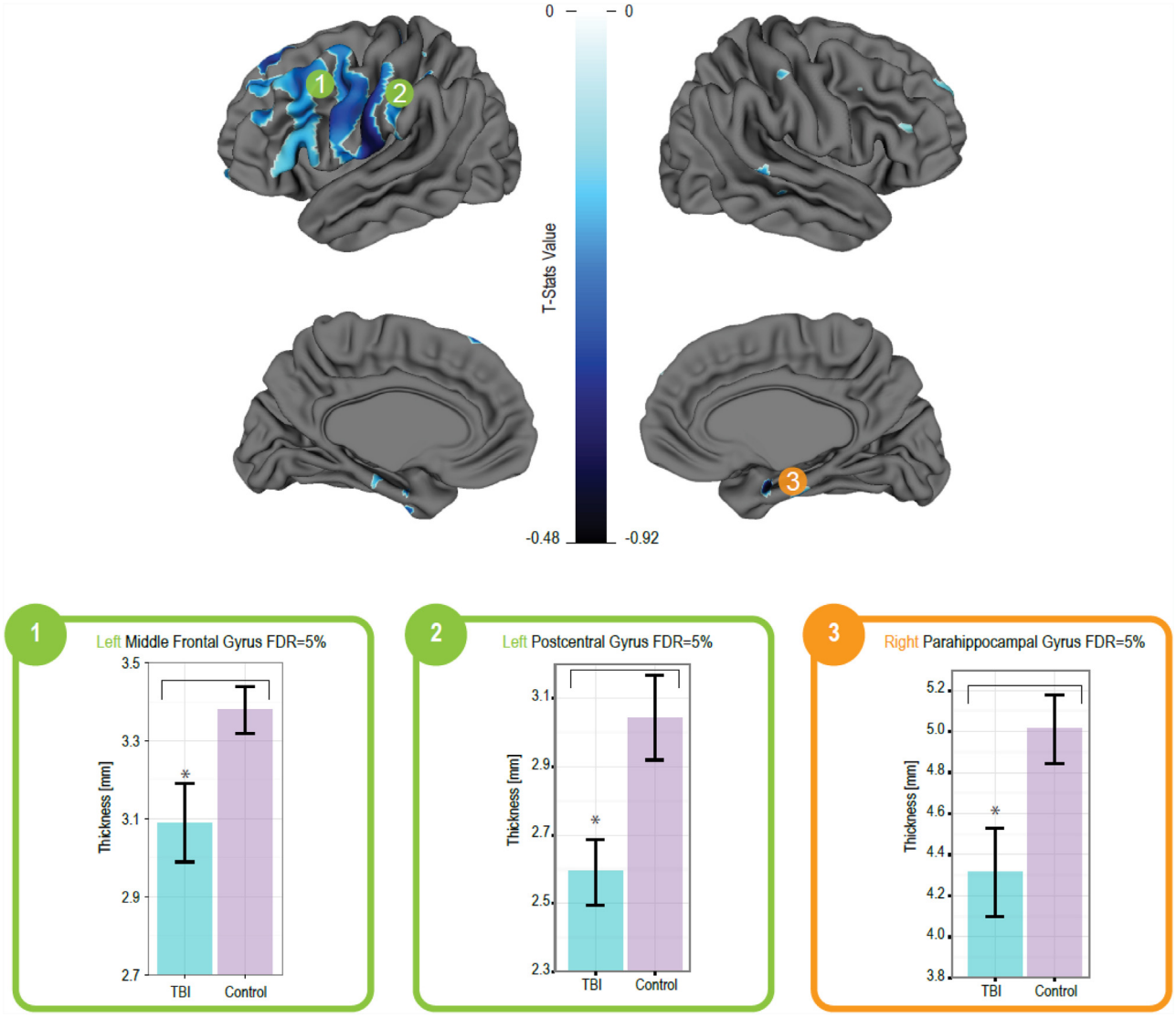


**Fig. 2.** Group differences in cortical thickness derived from a vertex-based analysis. T-statistics maps highlight regions with significant group effects. Bar graphs of selected voxels are plotted, and show significant thinning in the Concussion group for the left superior frontal gyrus (1), left postcentral gyrus (2), and the and right parahippocampal gyrus (4); localized thickening was found in the right superior temporal gyrus (3). *denotes significant differences using unpaired *t*-tests with FDR = 5%.

Structural studies of concussion point to long-term cortical thickness changes in frontal, parietal, temporal, and occipital regions up to 3 years post-injury [51] – chronic anatomical abnormalities that explain the lingering psychological symptomatology that persists in 10–20% of concussion patients. Other longitudinal studies of cortical thickness point to dynamic and temporally-dependent local thinning and thickening [52] of cortex, which suggests trajectories of recovery can vary between individuals, although how this relates to specific aspects of injury is currently unknown.

### 4.4. Concussion spares subcortical and cerebellar structures

Contrary to our initial hypotheses, we observed no significant differences in subcortical or cerebellar structures between our groups. This in part could be due to the heterogeneity of injury the variance in the biomechanical forces imparted by different types of injuries sparing these structures. Subcortical structures may be protected by their deep location in the brain while the cerebellum may be spared in a single concussion but affected by repetitive injury, particularly when the injury is caused by blast exposure [53]. Meabon and colleagues found that repetitive blast mTBI affects indicators of neural function and tractography measures in both humans and mice. The authors observed “a marked dose-response relationship between increasing numbers of blast-related mild TBIs and decreased metabolic activity specifically in the cerebellum”[53], with the authors concluding that the cerebellum is especially prone to repeated injury from blast pressure waves (primary component), rather than being particularly susceptible to secondary/tertiary components (e.g. coup/contrecoup), or showing marked changes after a single, non-blast injury, as seen here – such injury might spare this structure from alteration.

### 4.5. Limitations

The study should be considered with a number of caveats. First, it is possible participants failed to report a detailed history of concussive episodes and there is a chance they suffered more than one – it is known that sports-related concussions tend to be under-reported [54]. Second, it is possible even without a full-blown concussion there was a history of subconcussive but injurious blows that accumulate and contribute to neuromorphological change. Finally, there was a reasonably wide range of days since injury to scan. The

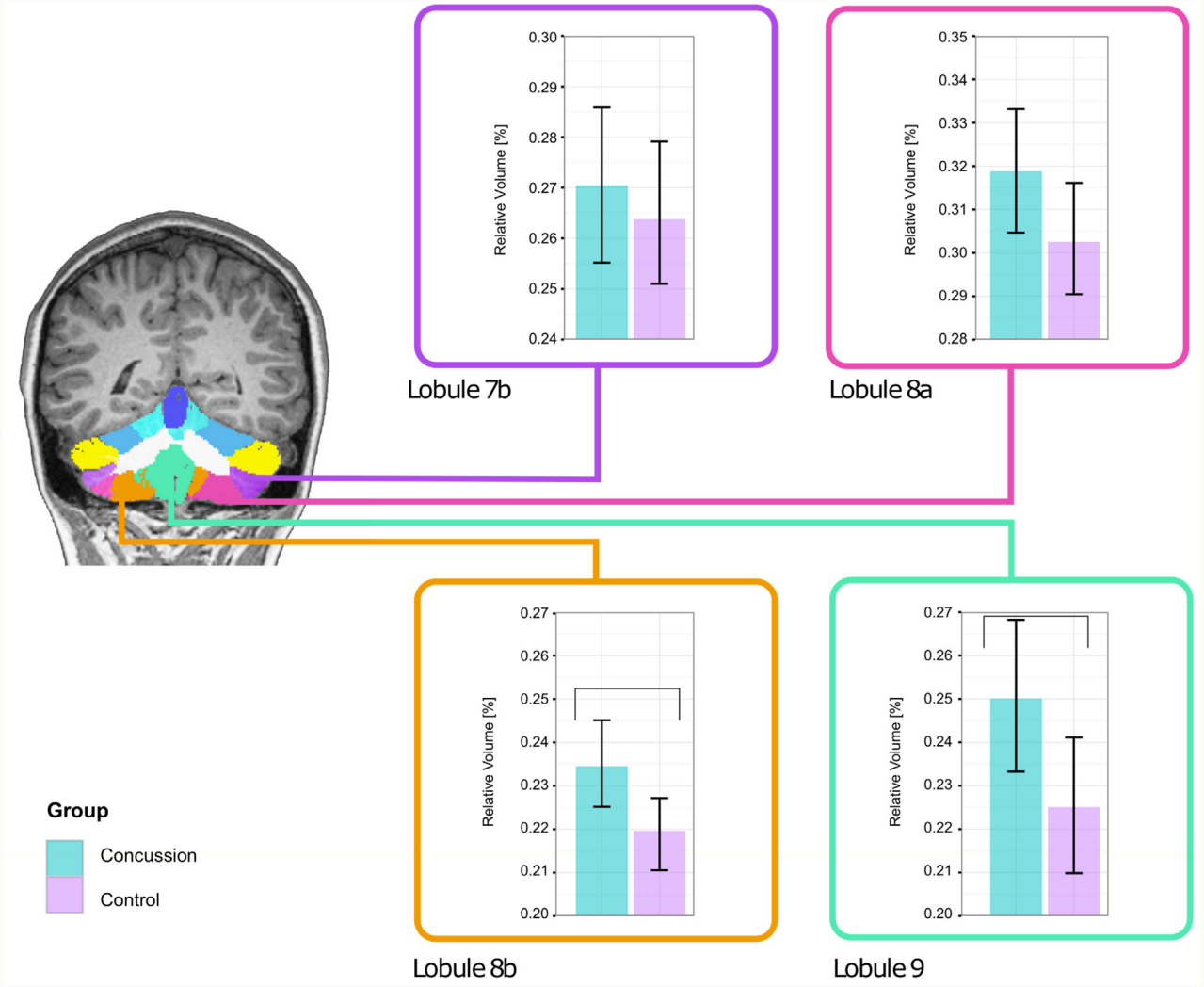


**Fig. 3.** Group contrasts for the cerebellar lobules – no significant difference were observed for any of the contrasts performed.

range spans the acute and subacute phase post-concussion – for future analyses, it would be interesting to use the days as a regressor to examine morphological changes related to that predictor.

## 5. Conclusion

Individuals in the acute and subacute stages of concussion exhibit diffuse and local patterns of altered white matter volume and cortical morphology. These findings corroborate existing research and accumulating evidence that following a single concussive episode there are significant and quantifiable changes in brain structure. Together, these findings suggest large-scale and almost-immediate remodelling of some cortical structures that underlie the neurobiological bases of the transient (and occasionally sustained) cognitive sequelae of concussion. These results emphasize the need to advocate for strong restrictions on 'return to play' policies, as a subsequent concussion is known to have an exponential impact on an already fragile brain [55].

## Author disclosure statement

No competing financial interests exist.

## Funding

This study was supported by a Defence Research and Development Canada contract (W7719-135182/001/TOR) to MJT and EWP.

## Acknowledgments

The authors thank Allison Bethune and Amanda Robertson for recruiting the participants and conducting the cognitive-behavioural assessments, the MRI technicians Ruth Weiss and Tammy Rayner, for all their support with data acquisition, Joel Pollock for assistance with graphic design, and Jason Lerch with statistical advice.

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