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Research article

Concussion induces focal and widespread neuromorphological changes

Dafna Sussman[a], Leodante da Costa[b], Mallar M. Chakravarty[c,d], Elizabeth W. Pang[e], Margot J. Taylor[f], Benjamin T. Dunkley[f,g,*]

[a] Physiology and Experimental Medicine, The Hospital for Sick Children, Toronto, Canada
[b] Division of Neurosurgery, Sunnybrook Hospital, Toronto, Canada
[c] Cerebral Imaging Centre, Douglas Mental Health University Institute, Montreal, Canada
[d] Departments of Psychiatry and Biological and Biomedical Engineering, McGill University, Montreal, Canada
[e] Neurology, The Hospital for Sick Children, Toronto, Canada
[f] Diagnostic Imaging, The Hospital for Sick Children, Toronto, Canada
[g] Department of Medical Imaging, University of Toronto, Toronto, Canada

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.

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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.

* Corresponding author at: Department of Diagnostic Imaging, Hospital for Sick Chidlren, 555, University Ave, Toronto, M5G 1X8, Canada.
E-mail addresses: ben.dunkley@sickkids.ca, btdunkley@gmail.com (B.T. Dunkley).

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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