



The first week after concussion: Blood flow, brain function and white matter microstructure



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ABSTRACT

Concussion is a major health concern, associated with short-term deficits in physical function, emotion and cognition, along with negative long-term health outcomes. However, we remain in the early stages of characterizing MRI markers of concussion, particularly during the first week post-injury when symptoms are most severe. In this study, 52 varsity athletes were scanned using Magnetic Resonance Imaging (MRI), including 26 athletes with acute concussion (scanned 1–7 days post-injury) and 26 matched control athletes. A comprehensive set of functional and structural MRI measures were analyzed, including cerebral blood flow (CBF) and global functional connectivity (Gconn) of grey matter, along with fractional anisotropy (FA) and mean diffusivity (MD) of white matter. An analysis comparing acutely concussed athletes and controls showed limited evidence for reliable mean effects of acute concussion, with only MD showing spatially extensive differences between groups. We subsequently demonstrated that the number of days post-injury explained a significant proportion of inter-subject variability in MRI markers of acutely concussed athletes. Athletes scanned at early acute injury (1–3 days) had elevated CBF and Gconn and reduced FA, but those scanned at late acute injury (5–7 days) had the opposite response. In contrast, MD showed a more complex, spatially-dependent relationship with days post-injury. These novel findings highlight the variability of MRI markers during the acute phase of concussion and the critical importance of considering the acute injury time interval, which has significant implications for studies relating acute MRI data to concussion outcomes.

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1. Introduction

Concussion is defined as traumatically-induced injury leading to altered brain function, in the absence of gross structural abnormalities. It is associated with impairments in physical function, cognition and emotion regulation (McCreary et al., 2003), which resolve within 7–10 days for most adults (McCrory et al., 2013). In the sport context, the medical guidelines for safe return-to-play (RTP) are mainly based on self-reported symptoms in response to physical exertion. However, these symptom-based guidelines only indirectly reflect the underlying

neurobiological changes that occur following a concussion. It is important to establish the acute pathophysiology of concussion, in order to better inform concussion management and safe RTP, as athletes with a history of concussion are at risk of re-injury (Abrahams et al., 2014) and have a higher risk for developing long-term cognitive impairments and depression (Guskiewicz et al., 2005; Guskiewicz et al., 2007; Gavett et al., 2011).

Magnetic Resonance Imaging (MRI) provides a versatile tool for objectively measuring brain function and structure. However, in order for MRI markers to inform clinical assessments and concussion management strategies, it is critical to establish acute post-concussion brain changes, particularly during the initial 1–7 days when most individuals are symptomatic. At present, most of our knowledge of the acute pathophysiology of concussion comes from rodent models (Giza and Hovda, 2001; Hovda et al., 1995; Giza et al., 2013). These studies have shown significant variation in metabolism, neural function and cerebral blood

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flow over the first 7–10 days, indicating that the neurobiological response to concussion is highly dependent on the time interval post-injury. While it is believed that concussion in humans shows a similar response, this has not yet been well established during the early acute phase of injury.

We are currently in the early stages of using MRI to characterize concussion pathophysiology in humans. Arterial spin labelling (ASL) has been used to measure cerebral blood flow (CBF), demonstrating reduced blood flow post-injury, but this modality has seen limited use to date (Hart et al., 2013; Meier et al., 2015). Functional MRI (fMRI) has been used to evaluate the neural activity of athletes with concussion based on fluctuations in cerebral blood-oxygenation, although these studies have mainly focused on the sub-acute interval from one week to one month post-injury (Slobounov et al., 2012; Zhang et al., 2010; Johnson et al., 2012). Despite most athletes being asymptomatic at this time, abnormalities in brain function have been identified, including increased task-related brain activity (Slobounov et al., 2012) and reduced functional connectivity in the resting brain (Johnson et al., 2012). Conversely, Diffusion tensor imaging (DTI) has been mainly used to investigate the long-term effects of concussion on the white matter microstructure in the brain. Most large-scale DTI studies have focused on retired athletes in collision sports, where long-term markers of white matter damage have been identified, including reduced fractional anisotropy (FA) and increased diffusivity within white matter tracts (Chappell et al., 2006; Zhang et al., 2006; Casson et al., 2014; Monaco and Tempel, 2015).

To date, investigations of acute concussion have been more limited, with most studies focusing on a single MRI modality. A study using arterial spin labelling (ASL) found no significant changes in cerebral blood flow (CBF) between 1 and 9 days post-injury (Meier et al., 2015), whereas a preliminary study of resting-state functional MRI (fMRI) found significant within-subject decreases in functional connectivity from 1 to 7 days post-injury (Zhu et al., 2015). In addition, a DTI-based study reported increasing FA and decreasing radial diffusivity in white matter tracts between 2 and 14 days post-injury, potentially indicating recovery from neural injury (Murugavel et al., 2014). These studies have shown significant within-subject brain changes at fixed time intervals during the acute phase of injury.

The present study extends these findings by examining multiple different MRI brain measures within a single group with acute concussion, including ASL, fMRI and DTI. This was investigated in a balanced sample of male and female athletes from a variety of different sports, to ensure that the findings are applicable to the wider sporting community. Given the limited literature on the acute phase of sport concussion, we first examined whether there are reliable differences in MRI markers of acutely concussed athletes relative to a group of control athletes, matched on age, sex and prior concussion history. Subsequently, motivated by the animal modelling literature, we investigated whether regressing MRI measures against the number of days post-injury at which they were acquired shows reliable effects among athletes with concussion and helps to account for inter-subject variability. The results of these analyses have significant implications for future concussion research, as they compare the sensitivity of different MRI markers during the first 7 days of injury, within a single well-characterized cohort.

2. Materials and methods

2.1. Study participants

A total of fifty-two (52) athletes were recruited for the current study, including 26 with acute concussion and 26 matched controls. Study participants were recruited from seven varsity teams at the University of Toronto (volleyball, hockey, soccer, football, rugby, basketball and lacrosse), via the institution's Sport Medicine Clinic. Twenty-six (26) athletes were recruited following a diagnosis of acute concussion by the referring physician, and scanned within 1–7 days post-injury. In

accordance with consensus guidelines (McCrory et al., 2013), athletes diagnosed with concussion were instructed to avoid physical exertion at this time, but were not otherwise restricted from daily activities. Following recruitment, athletes were evaluated using the sport concussion assessment tool 3 (SCAT3) (Guskiewicz et al., 2013), a standardized clinical tool which is used to evaluate symptoms, perform cognitive testing and assesses balance. For this study, we reported the total number of symptoms endorsed and total symptom severity (the sum of all symptom severity scores). We also reported scores from cognitive testing based on the standardized assessment of concussion (SAC) (McCrory et al., 1997), and balance based on the Balance Error Scoring System (BESS) (Guskiewicz, 2011). All SCAT3 scores were compared to pre-season baseline scores, which were collected from all athletes as part of the varsity sport concussion program.

Demographic information was collected, along with relevant clinical history, and each athlete with concussion was matched to a control athlete with no documented concussion in the 6 months prior to scanning. Controls were individually matched on sex and prior number of concussions, as multiple concussions are associated with long-term consequences (McCrory et al., 2013) and differences in brain function (Johnson et al., 2012). They were also matched on age (mean difference $\pm$ standard deviation: 0.1 ± 1.0 yrs.; $p = 0.39$, paired Wilcoxon test) to minimize potential developmental differences. The pre-season SCAT3 scores for controls were also collected, for comparison with the acutely concussed athletes. The study procedures were approved by the University of Toronto and St. Michael's Hospital institutional review boards, and all study participants provided written informed consent.

2.2. Magnetic resonance imaging

Participants were imaged at St. Michael's Hospital using an MRI system operating at 3 Tesla (Magnetom Skyra, Siemens, Erlangen, Germany) and standard 20-channel head receiver coil. In this study, Cerebral blood flow (CBF) was evaluated using Arterial Spin Labelling (ASL), which provided a voxel-wise map of resting CBF, measured in mL/100 g/min. Brain function was evaluated using resting-state fMRI. Global functional connectivity (Gconn) was estimated at each voxel by computing the functional connectivity with all other brain voxels, based on the Pearson correlation between voxel time series. Gconn was measured as the mean of all (positive) connectivity values. This is a well-established measure that quantifies total integrative function (Cole et al., 2012; Rubinov and Sporns, 2010). White matter microstructure was assessed using a DTI sequence followed by calculation of voxel-wise fractional anisotropy (FA), which reflects the degree that water diffusion has a "preferred direction", and mean diffusivity (MD), which reflects the overall rate of water diffusion. These measures are sensitive to local alterations in the cellular environment, including damage to cell membrane integrity and differences in axonal packing density. Structural brain imaging included a T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence. To screen for structural abnormalities, participants were also imaged with fluid attenuated inversion recovery imaging (FLAIR) and susceptibility-weighted imaging (SWI). Structural scans were reviewed in a 2-step procedure: (1) images were visually inspected by an MRI technologist and subsequently reviewed by a neuroradiologist and reported, if abnormalities were identified; (2) statistical testing for was performed, by obtaining global statistics on masked brain images (mean, variance and skew), generating a Z-score per concussed athlete relative to the control distribution, and identifying individuals significantly different at $p < 0.05$. No abnormalities (e.g., white matter hyper-intensities, contusions, micro-hemorrhage, or statistical outliers) were found for concussed athletes in this study.

Details of the MRI sequences and preprocessing steps are provided below.

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