Symptom correlates of cerebral blood flow following acute concussion

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ABSTRACT

Concussion is associated with significant symptoms within hours to days post-injury, including disturbances in physical function, cognition, sleep and emotion. However, little is known about how subjective impairments correlate with objective measures of cerebrovascular function following brain injury. This study examined the relationship between symptoms and cerebral blood flow (CBF) in individuals following sport-related concussion. Seventy university level athletes had CBF measured using Arterial Spin Labelling (ASL), including 35 with acute concussion and 35 matched controls and their symptoms were assessed using the Sport Concussion Assessment Tool 3 (SCAT3). For concussed athletes, greater total symptom severity was associated with elevated posterior cortical CBF, although mean CBF was not significantly different from matched controls ($p = 0.46$). Examining symptom clusters, athletes reporting greater cognitive symptoms also had lower frontal and subcortical CBF, relative to athletes with greater somatic symptoms. The "cognitive" and "somatic" subgroups also exhibited significant differences in CBF relative to controls ($p \leq 0.026$). This study demonstrates objective CBF correlates of symptoms in recently concussed athletes and shows that specific symptom clusters may have distinct patterns of altered CBF, significantly extending our understanding of the neurobiology of concussion and traumatic brain injury.

1. Introduction

Concussion is a form of mild traumatic brain injury (mTBI), which results in a cascade of pathophysiological changes and alterations in brain function. Although the majority of concussed adults typically recover within 10 days post-injury (McCrory et al., 2017), recovery timelines are highly variable between individuals. At present, clinical management and the determination of safe return-to-activity (i.e., school and sport) mainly rely on symptoms endorsement at rest, as well as symptom status in response to cognitive and physical exertion. Symptoms are assumed to indirectly reflect relatively subtle changes in brain physiology that occur following a concussion. However, there is limited research examining how symptoms are related to the acute pathophysiology of concussion. Moreover, although certain symptoms are frequently reported, including headache, dizziness, and difficulty concentrating (Kerr et al., 2016), the heterogeneity of symptoms post-concussion is well-documented (McCrory et al., 2017). The clinical

significance of this heterogeneity is being increasingly recognized, as patients endorsing different symptom types may experience different trajectories of injury and recovery (Collins et al., 2014; Iverson et al., 2004; Lau et al., 2011; McCrea et al., 2013). It is therefore important to characterize the relationship between symptom assessments and objective measures of brain physiology, to better understand the neurobiological mechanisms that may lead to subjective symptom impairments.

Cerebral blood flow (CBF) is highly sensitive to the effects of concussion and TBI (Len and Neary, 2011). In humans, CBF may be assessed non-invasively using arterial spin labelling (ASL). This procedure is a form of magnetic resonance imaging (MRI) which uses radio-frequency pulses to magnetically "tag" inflowing arterial blood, producing an endogenous tracer which can be used to quantify tissue perfusion. Using ASL, it has been demonstrated that CBF is reduced following concussion and mTBI (Ge et al., 2009; Grossman et al., 2013; Meier et al., 2015; Wang et al., 2015), although in some cases perfusion may

be initially unaltered or even elevated at early injury (Becelewski and Pierzchała, 2002; Churchill et al., 2017); these findings are also supported by animal model studies (Giza and Hovda, 2001; Giza and Hovda, 2014). Perfusion abnormalities in humans may persist after acute clinical symptoms have dissipated (Wang et al., 2015), with studies reporting decreased CBF relative to controls in the weeks to months following injury (Grossman et al., 2013; Kim et al., 2010).

Less is known about the relationship between CBF and the type and/ or severity of clinical symptoms, which include measures of physical and mental functioning. A study examining mTBI patients within 1 month post-injury reported regional hypo-perfusion in patients compared to controls, but more severe symptoms (particularly somatic symptoms, such as dizziness) were associated with higher regional CBF (Lin et al., 2016) in frontal and occipital lobes. Similarly, a study of persistent post-concussive symptoms in children reported elevated CBF in symptomatic individuals but decreased CBF in asymptomatic individuals, relative to controls (Barlow et al., 2016). These studies suggest that there may be reliable cerebral perfusion correlates of post-concussion symptoms following mild TBI throughout the concussion recovery timeline.

The present study extends these previous findings into the domain of sport concussion, by examining the relationship between CBF and symptoms in recently concussed athletes. This study specifically examined both total symptom severity and whether specific symptom clusters (i.e., somatic, cognitive, sleep/fatigue or emotional) were associated with different patterns of altered CBF. The investigation involved a balanced sample of male and female athletes in different sports, with contact and non-contact sport representation, to ensure that the findings are applicable to the wider sporting community. The ensuing analyses were conducted with the intention to improve our understanding of the relationship between post-concussion symptoms and objective markers of CBF regulation.

2. Materials and methods

2.1. Study participants

Seventy (70) athletes were recruited from inter-university sport teams from a single university (volleyball, hockey, soccer, football, rugby, basketball and lacrosse) through the institutional Sport Medicine Clinic. This included thirty-five (35) athletes with acute concussion and 35 matched controls, with no history of significant neurological or psychiatric conditions. Concussed athletes (19/35 female, mean $\pm$ SD age 20.3 $\pm$ 2.2 years, average of 1 concussion prior to the current acute injury, range 0 to 4) were recruited following a diagnosis of acute concussion by the referring physician, and imaged within 7 days post-injury (mean: 4.2 $\pm$ 1.3 days). The diagnosis was made by a staff physician in accordance to the definition set forth by the Concussion in Sport Group (McCrory et al., 2017). Each athlete with concussion was matched to a control athlete that had no documented concussions in the 6 months before scanning. Controls (19/35 female, mean age 20.3 $\pm$ 1.7 years, average history of 1 prior concussion, range 0 to 3) were individually matched to concussed athletes based on sex and prior number of concussions, as multiple concussions are associated with long-term consequences (McCrory et al., 2017) and differences in brain function (Johnson et al., 2012). Matching was also performed with respect to age (mean difference: 0.0 $\pm$ 1.2 years; $p = 0.94$, paired Wilcoxon test) to control for potential developmental differences, along with handedness (32/35 concussed were right-handed, 29/35 controls; $p = 0.508$, paired Wilcoxon test).

For all athletes participating in the study, pre-season baseline symptoms were assessed as part of standard clinical protocol at the university using the Sport Concussion Assessment Tool 3 (SCAT3) (Guskiewicz et al., 2013). The SCAT3 also includes cognitive indices based on the Standardized Assessment of Concussion (SAC) (McCrea et al., 1997) and balance testing based on the Balance Error Scoring

System (BESS) (Bell et al., 2011). The SCAT3 is a widely-used tool for the clinical assessment of concussion within the sports context, with extensive validation and evidence of good evidence of reliability and specificity (Guskiewicz et al., 2013; McCrory et al., 2013). For acutely concussed athletes, SCAT3 assessment was also conducted within 7 days post-injury (mean: 3.6 $\pm$ 1.2 days). This study was carried out in accordance with the recommendations of the Canadian Tri-Council Policy Statement 2 (TCPS2) and the research ethics boards of the University of Toronto and St. Michael's Hospital, with written informed consent from all participants. All participants gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the research ethics boards of the University of Toronto and St. Michael's Hospital.

2.2. Magnetic resonance imaging

Participants were imaged at St. Michael's Hospital using a research-dedicated MRI system operating at 3 Tesla (Magnetom Skyra, Siemens, Erlangen, Germany) and standard 20-channel head receiver coil. Structural brain imaging included a 3D T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence. Cerebral blood flow (CBF) was evaluated using 2D pulsed Arterial Spin Labelling (ASL) with the PICORE QUIPSS II sequence and oblique axial slices. This provided a voxel-wise map of resting CBF, averaged over 45 tag-control pairs, measured in mL/100 g/min (see Supplementary Text 1 for full details of MRI scan parameters and CBF estimation).

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: images were visually inspected by an MRI technologist and subsequently reviewed by a neuroradiologist and reported, if abnormalities were identified. Statistical testing was also performed, by obtaining mean, variance and skew of masked brain images, generating a Z-score per concussed athlete relative to the control distribution and identifying individuals significantly different at $p < 0.05$. No abnormalities (white matter hyper-intensities, contusions, micro-hemorrhage, or statistical outliers) were found for either concussed athletes or controls in this study.

2.3. Clinical and demographic data

Analyses of SCAT3 symptoms included total symptom severity, obtained by summing across a 22-item symptom scale, each with a 7-point Likert scale rating (Guskiewicz et al., 2013). In addition, total severity was examined separately within four symptom clusters: somatic (Headache, Pressure in head, Neck Pain, Nausea/vomiting, Dizziness, Blurred vision, Balance problems, Sensitivity to light, Sensitivity to noise), cognitive (Feeling slowed down, Feeling "in a fog", "Don't feel right", Difficulty concentrating, Difficulty remembering, Confusion), fatigue and sleep problems (Fatigue/low energy, Drowsiness, Trouble falling asleep) and emotion (More emotional, Irritability, Sadness, Nervous/anxious). Initial testing determined whether total symptom severity was elevated at acute concussion, relative to both baseline scores and matched controls, via non-parametric paired Wilcoxon tests. Similar analyses were conducted for each of the individual symptom clusters (somatic, cognitive, sleep/fatigue, emotion).

Based on prior literature, there is evidence that baseline SCAT3 scores show significant variability between athletes (Covassin et al., 2012). However, it is unknown whether the change in symptoms from baseline to acute injury is significantly different from the absolute severity score, as both show comparable sensitivity in detecting concussion (Hänninen et al., 2017). A subsequent analysis therefore measured the correlation between total symptom severity at acute injury and the difference in total severity scores from baseline to acute injury. An additional set of analyses tested whether total symptom severity was significantly correlated with age, sex, number of prior concussions and

number of days post-injury (for both MRI scanning and SCAT3 assessment), along with individual symptom clusters. Correlations were measured using non-parametric Spearman correlations and bootstrapped 95% confidence intervals (95% CIs) were reported, based on 1000 resampling iterations. For all analyses of clinical and demographic data, multiple comparison correction was conducted at a False Discovery Rate of 0.05.

2.4. Neuroimaging and symptoms

It was then determined whether total symptom severity reliably accounted for inter-subject variability in CBF among acutely concussed athletes. Analyses were done using ordinary least squares linear regression, with CBF values regressed against symptom severity for each brain voxel. Significance was evaluated by bootstrap resampling to obtain confidence bounds on regression coefficients (1000 iterations) and reporting brain regions where bootstrapped 95% CIs did not enclose zero effect. Confidence bounds were adjusted for multiple comparisons by thresholding voxels where 99.5% CIs did not enclose zero ($p = 0.005$ 2-tailed significance) and cluster-size thresholding at $p = 0.05$, using the Analysis of Functional Neuroimaging (AFNI, afni.nimh.nih.gov) program *3dFWHMx* to estimate spatial smoothness of the images and using these values as inputs to AFNI *3dClustSim* to estimate the corresponding cluster-size threshold. For significant voxels, the effect size was reported in terms of the bootstrap ratio, computed as the bootstrapped mean divided by its standard error. For comparison with uninjured athletes, the mean CBF value was computed over all significant voxels, for each participant, in both concussed and control groups. Bootstrapped resampling was then performed (1000 iterations), to estimate the mean difference in CBF between concussed athletes and controls, including the 95% CI and empirical *p*-value. The mean CBF values were plotted for both control and concussed groups, along with group mean CBF and bootstrapped 95% CIs of the group means.

Two symptom clusters were identified (somatic and cognitive), which were significantly altered at acute concussion compared to matched controls (see clinical and demographic results below). The absolute severity scores of somatic and cognitive clusters were highly collinear with total symptom severity (Pearson correlations of 0.98 and 0.97, respectively) indicating that they have near-identical relationships with CBF. A second analysis therefore tested whether patients with high scores in the cognitive subscale relative to the somatic subscale (or vice-versa) had a distinct pattern of altered CBF. This was done by z-scoring symptom scores of the concussed athlete group for each cluster, then measuring the difference in z-scored values (cognitive − somatic) per patient, which was uncorrelated with total symptom severity (Pearson correlation of − 0.03). These values were regressed against voxel-wise CBF, with significant brain regions identified as indicated above. For comparison with matched controls, the mean CBF value was computed within significant voxels, for participants in both concussed and control cohorts. A bootstrap analysis was then performed (1000 iterations) to estimate the difference in mean CBF between concussed athletes and controls within these brain regions, including 95% CIs and empirical *p*-values. In addition, concussed subgroups with (cognitive > somatic) and (somatic > cognitive) symptoms were separately compared to the control cohort using bootstrap analyses. The mean CBF values were plotted for controls and both concussed subgroups, along with group mean CBF values and bootstrapped 95% CIs of the group means.

The concussed athletes in this study were scanned at different times post-injury, ranging from 1 to 7 days. In previous work, neuroimaging markers of acute concussion were shown to be significantly dependent on the post-injury time interval (Churchill et al., 2017). To test whether this is a significant confound in the present study, an additional set of analyses compared regression coefficients, when symptoms were regressed against (1) CBF data (i.e., as described in the above paragraph) and (2) CBF data, after first regressing out the effects of days post-injury

Table 1

participant demographics. Age is reported as mean ± SD, all other distributions are reported as median [min, max]. Symptom scores with ** denote significant difference at acute injury, relative to both within-subject baseline and controls.

	Control	Concussion	
Age (mean ± SD)	20.3 ± 1.7	20.3 ± 2.2	
Female	19/35	19/35	
Previous concussions	0 [0,3]	1 [0,4]	
		Baseline	Acute
Symptom severity			
Total	3 [0,29]	3 [0,24]	11 [0,90]**
Somatic	0 [0,17]	1 [0,9]	7 [0,36]**
Cognitive	0 [0,7]	0 [0,9]	3 [0,27]**
Sleep/Fatigue	0 [0,5]	1 [0,7]	2 [0,14]
Emotional	0 [0,4]	0 [0,4]	0 [0,17]
Cognitive and balance			
Orientation	5 [4,5]	5 [4,5]	5 [4,5]
Immediate memory	15 [9,15]	15 [13,15]	15 [13,15]
Concentration	3 [1,5]	4 [2,5]	4 [2,5]
Delayed memory	4 [1,5]	5 [0,5]	4 [1,5]
Balance total errors	1 [0,10]	3 [0,12]	3 [0,12]

(i.e., analyzing the residuals). Differences in voxelwise regression coefficients were calculated between (1) and (2), with significance determined via bootstrap resampling (1000 iterations). As in the previous sections, the adjusted 95% CIs were calculated on the paired differences, and brain regions reported where confidence bounds did not enclose zero effect.

3. Results

3.1. Clinical and demographic data

Table 1 summarizes participant demographics and SCAT3 scores. Concussed athletes had significantly higher symptom severity scores relative to their baseline (mean change ± standard error: 17.0 ± 3.9) and relative to matched controls (mean difference: 16.9 ± 4.2), both with $p < 0.001$. For symptom clusters, only the somatic and cognitive clusters were significantly increased relative to baseline (8.0 ± 1.4 and 4.6 ± 1.2, respectively) and controls (8.6 ± 1.7 and 5.0 ± 1.3, respectively), with all tests having $p < 0.001$ and remaining significant after multiple comparison correction. In contrast, the sleep/fatigue and emotion clusters were not significantly different after multiple comparison correction, relative to baseline (1.3 ± 0.6 and 1.2 ± 0.6, $p = 0.16$ and 0.12 respectively) and controls (1.7 ± 0.7 1.5 ± 0.8, $p = 0.036$ and 0.30 respectively).

At acute injury, the SAC and BESS subscales showed no significant differences relative to baseline or matched controls ($p > 0.23$, all tests). In addition, the severity of acute symptoms was not significantly correlated with age (Spearman rho $\rho = 0.05$, $p = 0.76$), sex ($\rho = 0.19$, $p = 0.27$), history of concussion ($\rho = -0.07$, $p = 0.70$) or number of days post-injury, either for scanning ($\rho = -0.11$, $p = 0.51$) or for SCAT3 assessment ($\rho = -0.07$, $p = 0.70$). Total symptom severity at acute injury was highly correlated with the difference in severity scores from baseline to acute injury ($\rho = 0.89$, $p < 0.001$). Moreover, all symptom clusters were highly correlated with total symptom severity at acute injury, including somatic ($\rho = 0.96$), cognitive ($\rho = 0.87$), sleep/fatigue ($\rho = 0.84$) and emotion ($\rho = 0.73$), all $p < 0.001$ and remaining significant after multiple comparison correction.

3.2. Neuroimaging and symptoms

Fig. 1A depicts the results of regressing CBF against total symptom severity scores. Higher symptom severity was associated with significant increases in posterior cerebral perfusion, including the superior
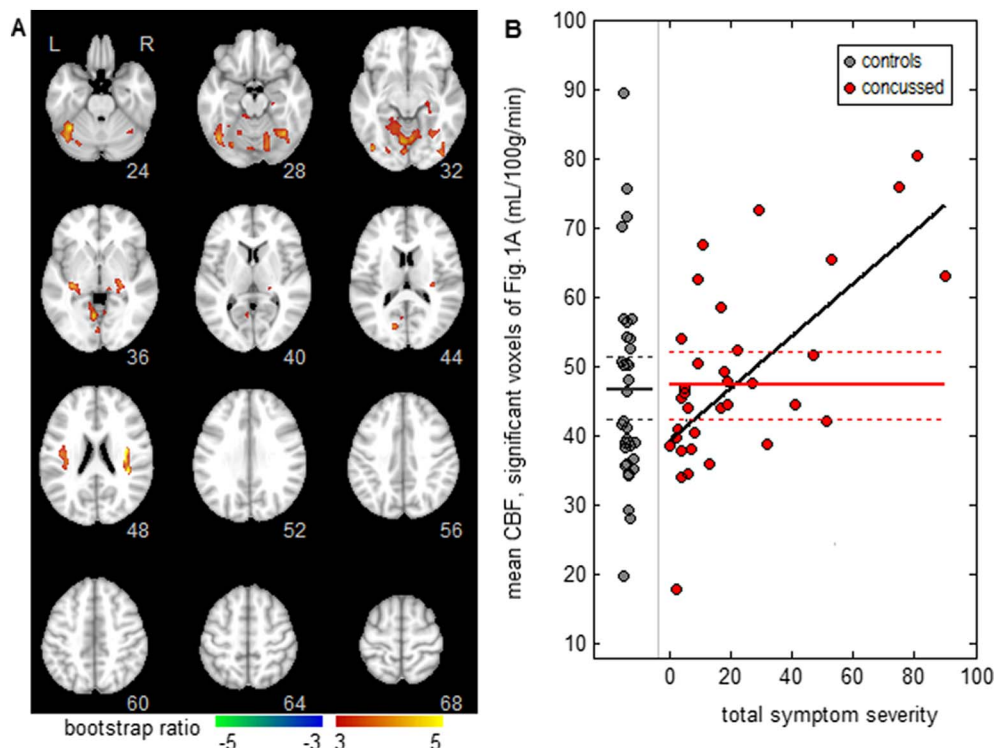
Fig. 1. Cerebral blood flow (CBF) correlates of total symptom severity scores at acute injury. (A) Brain regions significantly associated with total symptom severity. (B) Mean CBF of significant voxels of panel A, plotted for individual concussed athletes against total symptom severity, along with matched controls. The mean (solid horizontal line) and bootstrapped 95% CIs of the mean (dashed lines) are plotted for both concussed athletes (red) and controls (grey), along with the regression line of best fit for concussed athletes (black line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cerebellum, occipital lobe and cuneus. Increased CBF was also observed subcortically in the right parahippocampal gyrus and bilateral insula. Fig. 1B plots mean CBF values (of significant brain regions in Fig. 1A) against symptom severity for concussed athletes, along with the CBF values of matched controls. Although concussed athletes show a modest relationship between CBF and symptom severity in these brain regions ($R^2 = 0.35$), mean CBF values of concussed athletes were not significantly different from controls, with mean difference + 0.45 mL/

100 g/min (95% CI: − 6.32 to 7.46; $p = 0.46$, bootstrap analysis).

Fig. 2A depicts the results of regressing CBF against the difference in severity of (cognitive – somatic) symptom subscales, showing much more spatially extensive effects than total symptom severity. Higher cognitive symptoms (relative to somatic symptoms) were associated with reduced CBF frontally, including bilateral orbitofrontal cortex, middle frontal cortex and supplementary motor area, along with anterior cingulate. In addition, extensive subcortical effects were found
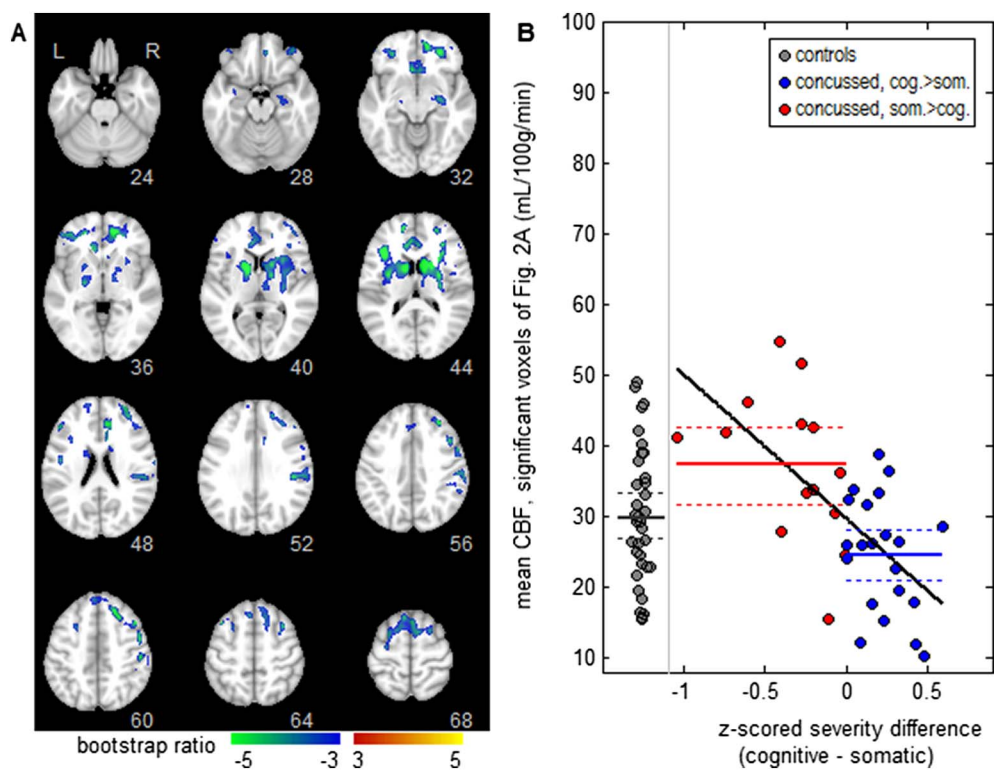

Fig. 2. Cerebral blood flow (CBF) correlates of symptom clusters at acute injury. (A) Brain regions significantly associated with the difference in z-scored severity for symptom clusters (cognitive – somatic). (B) Mean CBF of significant voxels of panel A, plotted for individual concussed athletes against total symptom severity, along with matched controls. The mean (solid horizontal line) and bootstrapped 95% CIs of the mean (dashed lines) are plotted for concussed athletes with cognitive > somatic (blue), concussed athletes with somatic > cognitive (red) and matched controls (grey), along with the regression line of best fit for all concussed athletes (black line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

bilaterally in the caudate, extending into the insula. Fig. 2B plots mean CBF values (of significant brain regions in Fig. 2A) against symptom severity for concussed athletes, along with the CBF values of matched controls. As in Fig. 1, concussed athletes show a modest relationship between CBF and symptom severity in these brain regions ($R^2 = 0.39$), but mean CBF values of concussed athletes were not significantly different from controls, with a mean difference of -0.72 mL/100 g/min (95% CI: -5.58 to 4.13; $p = 0.62$, bootstrap analysis). However, examining patient subgroups separately, athletes with (cognitive > somatic) had significantly lower CBF compared to controls with a mean difference of -5.70 mL/100 g/min (95% CI: -10.98 to -0.92; $p = 0.014$), while athletes with (somatic > cognitive) had significantly higher CBF with a mean difference of $+7.04$ mL/100 g/min (95% CI: 1.00 to 13.17; $p = 0.026$). Hence, the patient subgroups show opposite effects of concussion on CBF, leading to non-significant differences from controls if these subgroups are combined.

An additional set of analyses tested for confounding effects of days post-injury, by determining whether controlling for this covariate significantly altered voxelwise statistics on regression coefficients, for both total symptom severity and the difference in severity of (cognitive – somatic) symptom subscales. After cluster-size correction, this had a non-significant effect for both analyses. Thus, the effects of day post-injury do not appear to be a significant confound for symptom analyses.

4. Discussion

This study examined the relationship between CBF and symptoms among recently concussed athletes. The primary findings were modest but reliable associations between subjective, self-reported symptoms and objective MRI-based measures of CBF. This provides preliminary evidence supporting a potential objective, neurobiological basis for self-reported symptoms. Overall, greater symptom severity was associated with increased CBF, primarily in posterior cortical and cerebellar regions. Moreover, symptom clusters showed distinct patterns of cerebral perfusion, as individuals with relatively high cognitive symptom scores had lower frontal CBF and subcortical CBF in the caudate and insula, compared to those with relatively high somatic symptom scores.

The elevated CBF among athletes with higher overall symptom complaints at acute injury is consistent with prior studies of mTBI, where individuals with persistent post-concussive symptoms had elevated CBF (Barlow et al., 2016; Lin et al., 2016). The findings of the present study, in which the effects of total symptom severity were spatially limited to posterior brain regions (Fig. 1A), are consistent with occipital hyper-perfusion reported for mTBI patients with more severe symptoms (Lin et al., 2016). In comparison, global elevations in CBF were reported for children with mTBI (Barlow et al., 2016), suggesting that the effects of concussion on brain perfusion may be more spatially extensive in younger patients.

The present study also examined clusters of somatic and cognitive symptom complaints. Although these subscales were highly correlated with total symptom severity, the relative difference of (cognitive – somatic) severities yielded highly robust associations with CBF in acutely concussed athletes. Consistent regional differences in CBF were identified between subgroups, including frontal and subcortical areas (Fig. 2A). Interestingly, individuals with (cognitive > somatic) symptoms and those with (somatic > cognitive) symptoms were significantly different from matched controls but showed opposite directions of effect. This suggests that combining patient subgroups may obscure CBF abnormalities that are unique to specific symptom clusters. For the "somatic" subgroup, elevated CBF indicates that this cluster shows similar effects as total symptom severity (i.e., increased CBF). This is expected, given that the somatic symptom cluster has a higher correlation with total symptoms, compared to the cognitive cluster.

While the effects of mTBI on cerebrovascular function has been described (Len and Neary, 2011), much remains unknown about how variations in CBF and autoregulation relate to specific functional

disturbances. For the "somatic" subgroup, a potential explanation for elevated CBF is that individuals endorsing higher somatic complaints have greater post-concussion neuroinflammatory response. The hypothesis is supported by prior literature in which elevated CBF has been reported following neurological insult such as stroke (Marchal et al., 1996), an effect which may be mediated via neuroinflammatory pathways (Fassbender et al., 2001). Taken with the present findings, this indicates a potential physiological basis for elevated somatic symptoms, which should be examined in future research by combining neuroimaging with serum markers of inflammation and neuronal injury (Di Battista et al., 2016a; Di Battista et al., 2016b).

Conversely, the reduced perfusion for individuals in the "cognitive" subgroup indicates that these symptoms are potentially reflective of reduced oxygen delivery to grey matter (Toledo et al., 2012). In particular, reduced frontal CBF is consistent with impairments in higher-level cognition. However, it is presently unclear whether the reduced CBF occurred in response to decreased neural activity (i.e., indicating impaired neural metabolism), or it was due to impaired blood flow autoregulation, with maintained neural activity (i.e., indicating cerebral ischemia). Extensive subcortical effects were also seen, including caudate and insula, suggesting that CBF regulation in these regions is also highly sensitive to symptom type. This is of particular interest, given that these regions, along with the anterior cingulate, are implicated in interoception, self-monitoring and emotion awareness (Critchley, 2005; Lane et al., 1998), which are relevant to symptom reporting. The present findings are also supported by prior TBI literature showing sub-cortical perfusion changes in the thalamus (Ge et al., 2009), which exhibits high anatomical connectivity with the insular cortex. These results indicate that subcortical perfusion in the identified brain regions may be a key biomarker of specific types of post-concussion symptom impairments.

The observed relationship between cerebral perfusion and post-concussion symptoms may be influenced by premorbid factors, time of imaging and the method or tool to ascertain symptom status. The present study showed that controlling for days post-injury had no significant impact on relationship between symptoms and CBF. However, (Meier et al., 2015) analyzed insular CBF for a group of concussed male football players, and found no significant relationship with symptoms from 1 day to 1 week post-injury, but reported negative correlations at 1 month post-injury. This suggests that relationships between symptoms and CBF may be altered beyond the early phase of injury. Similarly, male and female athletes show significant differences in symptom presentation and autonomic response to concussion (Hutchison et al., 2017). These findings collectively indicate that other demographic factors may influence the relationship between CBF, concussion and self-reported symptoms. Nonetheless, the consistency of the present findings with other mTBI literature suggests that common biomarkers of post-concussion symptoms are identifiable.

The findings of this study provide strong initial neurobiological evidence for distinct subgroups within the "global" clinical syndrome of concussion, in which different symptom subgroups show distinct patterns of altered CBF. These findings are aligned with prior concussion literature, which recommends that researchers consider distinct patient subgroups, which may lead to beneficial targeted interventions (Collins et al., 2014). This study shows significant associations between subjective symptom scores and objective measures of CBF, significantly extending our understanding of the neurobiology of sport concussion and associated changes in cerebral perfusion.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2017.07.019.

References

Barlow, K.M., Marcil, L.D., Dewey, D., Carlson, H.L., MacMaster, F.P., Brooks, B.L., Lebel, R.M., 2016. Cerebral perfusion changes in post-concussion syndrome: a prospective controlled cohort study. J. Neurotrauma.

Becelewski, J., Pierzchała, K., 2002. Cerebrovascular reactivity in patients with mild head injury. Neurol. Neurochir. Pol. 37, 339–350.

Bell, D.R., Guskiewicz, K.M., Clark, M.A., Padua, D.A., 2011. Systematic review of the balance error scoring system. Sports Health: A Multidisciplinary Approach 3, 287–295.

Churchill, N.W., Hutchison, M.G., Richards, D., Leung, G., Graham, S.J., Schweizer, T.A., 2017. The first week after concussion: blood flow, brain function and white matter microstructure. NeuroImage: Clinical 14, 480–489.

Collins, M.W., Kontos, A.P., Reynolds, E., Murawski, C.D., Fu, F.H., 2014. A comprehensive, targeted approach to the clinical care of athletes following sport-related concussion. Knee Surg. Sports Traumatol. Arthrosc. 22, 235–246.

Covassin, T., Elbin, R.J., Harris, W., Parker, T., Kontos, A., 2012. The role of age and sex in symptoms, neurocognitive performance, and postural stability in athletes after concussion. Am. J. Sports Med. 40 (6), 1303–1312.

Critchley, H.D., 2005. Neural mechanisms of autonomic, affective, and cognitive integration. J. Comp. Neurol. 493, 154–166.

Di Battista, A.P., Rhind, S.G., Richards, D., Churchill, N., Baker, A.J., Hutchison, M.G., 2016a. Altered blood biomarker profiles in athletes with a history of repetitive head impacts. PLoS One 11, e0159929.

Di Battista, A.P., Rizoli, S.B., Lejnieks, B., Min, A., Shiu, M.Y., Peng, H.T., Baker, A.J., Hutchison, M.G., Churchill, N., Inaba, K., 2016b. Sympathoadrenal activation is associated with acute traumatic coagulopathy and endotheliopathy in isolated brain injury. Shock 46, 96 (Augusta, Ga.).

Fassbender, K., Hodapp, B., Rossol, S., Bertsch, T., Schmeck, J., Schütt, S., Fritzinger, M., Horn, P., Vajkoczy, P., Kreisel, S., 2001. Inflammatory cytokines in subarachnoid haemorrhage: association with abnormal blood flow velocities in basal cerebral arteries. J. Neurol. Neurosurg. Psychiatry 70, 534–537.

Ge, Y., Patel, M.B., Chen, Q., Grossman, E.J., Zhang, K., Miles, L., Babb, J.S., Reaume, J., Grossman, R.I., 2009. Assessment of thalamic perfusion in patients with mild traumatic brain injury by true FISP arterial spin labelling MR imaging at 3T. Brain Inj. 23, 666–674.

Giza, C., Hovda, D., 2001. The neurometabolic cascade of concussion. J. Athl. Train. 36, 228.

Giza, C.C., Hovda, D.A., 2014. The new neurometabolic cascade of concussion. Neurosurgery 75, S24.

Grossman, E., Jensen, J., Babb, J., Chen, Q., Tabesh, A., Fieremans, E., Xia, D., Inglese, M., Grossman, R., 2013. Cognitive impairment in mild traumatic brain injury: a longitudinal diffusional kurtosis and perfusion imaging study. Am. J. Neuroradiol. 34, 951–957.

Guskiewicz, K., Register-Mihalik, J., McCrory, P., McCrea, M., Johnston, K., Makdissi, M., Meeuwisse, W., 2013. Evidence-based approach to revising the SCAT2: introducing the SCAT3. Br. J. Sports Med. 47, 289–293.

Hänninen, T., Parkkari, J., Tuominen, M., Iverson, G.L., Öhman, J., Vartiainen, M., Luoto, T.M., 2017. Interpreting change on the SCAT3 in professional ice hockey players. Am. J. Sports Med. 20 (5), 424–431.

Hutchison, M., Mainwaring, L., Senthinathan, A., Churchill, N., Thomas, S., Richards, D.,

2017. Psychological and physiological markers of stress in concussed athletes across recovery milestones. J. Head Trauma Rehabil. 32, E38–48.

Iverson, G.L., Gaetz, M., Lovell, M.R., Collins, M.W., 2004. Relation between subjective fogginess and neuropsychological testing following concussion. J. Int. Neuropsychol. Soc. 10, 904–906.

Johnson, B., Zhang, K., Gay, M., Horovitz, S., Hallett, M., Sebastianelli, W., Slobounov, S., 2012. Alteration of brain default network in subacute phase of injury in concussed individuals: resting-state fMRI study. NeuroImage 59, 511–518.

Kerr, Z.Y., Zuckerman, S.L., Wasserman, E.B., Covassin, T., Djoko, A., Dompier, T.P., 2016. Concussion symptoms and return to play time in youth, high school, and college American football athletes. JAMA Pediatr. 170, 647–653.

Kim, J., Whyte, J., Patel, S., Avants, B., Europa, E., Wang, J., Slattery, J., Gee, J.C., Coslett, H.B., Detre, J.A., 2010. Resting cerebral blood flow alterations in chronic traumatic brain injury: an arterial spin labeling perfusion FMRI study. J. Neurotrauma 27, 1399–1411.

Lane, R.D., Reiman, E.M., Axelrod, B., Yun, L.-S., Holmes, A., Schwartz, G.E., 1998. Neural correlates of levels of emotional awareness: evidence of an interaction between emotion and attention in the anterior cingulate cortex. J. Cogn. Neurosci. 10, 525–535.

Lau, B.C., Collins, M.W., Lovell, M.R., 2011. Sensitivity and specificity of subacute computerized neurocognitive testing and symptom evaluation in predicting outcomes after sports-related concussion. Am. J. Sports Med. 39, 1209–1216.

Len, T., Neary, J., 2011. Cerebrovascular pathophysiology following mild traumatic brain injury. Clin. Physiol. Funct. Imaging 31, 85–93.

Lin, C.-M., Tseng, Y.-C., Hsu, H.-L., Chen, C.-J., Chen, D.Y.-T., Yan, F.-X., Chiu, W.-T., 2016. Arterial spin labeling perfusion study in the patients with subacute mild traumatic brain injury. PLoS One 11, e0149109.

Marchal, G., Furlan, M., Beaudouin, V., Rioux, P., Hauttement, J.L., Serrati, C., de la Sayette, V., Le Doze, F., Viader, F., Derlon, J.M., 1996. Early spontaneous hyperperfusion after stroke. Brain 119, 409–419.

McCrea, M., Kelly, J., Kluge, J., Ackley, B., Randolph, C., 1997. Standardized assessment of concussion in football players. Neurology 48, 586–588.

McCrea, M., Guskiewicz, K., Randolph, C., Barr, W.B., Hammeke, T.A., Marshall, S.W., Powell, M.R., Ahn, K.W., Wang, Y., Kelly, J.P., 2013. Incidence, clinical course, and predictors of prolonged recovery time following sport-related concussion in high school and college athletes. J. Int. Neuropsychol. Soc. 19, 22–33.

McCrory, P., Meeuwisse, W., Aubry, M., Cantu, B., Dvořák, J., Echemendia, R., Sills, A., 2013. Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. Br. J. Sports Med. 47, 250–258.

McCrory, P., Meeuwisse, W., Dvořák, J., Aubry, M., Bailes, J., Broglio, S., Cantu, R.C., Cassidy, D., Echemendia, R.J., Castellani, R.J., Davis, G.A., Ellenbogen, R., Emery, C., Engebretsen, L., Feddermann-Demont, N., Giza, C.C., Guskiewicz, K.M., Herring, S., Iverson, G.L., Johnston, K.M., Kissick, J., Kutcher, J., Leddy, J.J., Maddocks, D., Makdissi, M., Manley, G.T., McCrea, M., Meehan, W.P., Nagahiro, S., Patricios, J., Putukian, M., Schneider, K.J., Sills, A., T., C.H., Turner, M., Vos, P.E., 2017. Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016. Br. J. Sports Med. 51, 838–847.

Meier, T., Bellgowan, P., Singh, R., Kuplicki, R., Polanski, D., Mayer, A., 2015. Recovery of cerebral blood flow following sports-related concussion. JAMA Neurol. 72, 530–538.

Toledo, E., Lebel, A., Becerra, L., Minster, A., Linnman, C., Maleki, N., Borsook, D., 2012. The young brain and concussion: imaging as a biomarker for diagnosis and prognosis. Neurosci. Biobehav. Rev. 36 (6), 1510–1531.

Wang, Y., Nelson, L.D., LaRoche, A.A., Pfaller, A.Y., Nencka, A.S., Koch, K.M., McCrea, M.A., 2015. Cerebral blood flow alterations in acute sport-related concussion. J. Neurotrauma.