Recovery of Cerebral Blood Flow Following Sports-Related Concussion

Timothy B. Meier, PhD; Patrick S. F. Bellgowan, PhD; Rashmi Singh, PhD; Rayus Kuplicki, PhD; David W. Polanski, MS, ATC, LAT; Andrew R. Mayer, PhD

IMPORTANCE Animal models suggest that reduced cerebral blood flow (CBF) is one of the most enduring physiological deficits following concussion. Despite this, longitudinal studies documenting serial changes in regional CBF following human concussion have yet to be performed.

OBJECTIVE To longitudinally assess the recovery of CBF in a carefully selected sample of collegiate athletes and compare time course of CBF recovery with that of cognitive and behavioral symptoms.

DESIGN, SETTING, AND PARTICIPANTS A cohort of collegiate football athletes (N = 44) participated in this mixed longitudinal and cross-sectional study at a private research institute specializing in neuroimaging between March 2012 and December 2013. Serial imaging occurred approximately 1 day, 1 week, and 1 month postconcussion for a subset of participants (n = 17). All athletes reported no premorbid mood disorders, anxiety disorders, substance abuse, or alcohol abuse.

MAIN OUTCOMES AND MEASURES Arterial spin labeling magnetic resonance imaging was used to collect voxelwise relative CBF at each visit. Neuropsychiatric evaluations and a brief cognitive screen were also performed at all 3 points. Clinicians trained in sports medicine provided an independent measure of real-world concussion outcome (ie, number of days withheld from competition).

RESULTS The results indicated both cognitive (simple reaction time) and neuropsychiatric symptoms at 1 day postinjury that resolved at either 1 week (cognitive; P < .005) or 1 month (neuropsychiatric; P < .005) postinjury. Imaging data suggested both cross-sectional (ie, healthy vs concussed athletes; P < .05) and longitudinal (1 day and 1 week vs 1 month postinjury; P < .001) evidence of CBF recovery in the right insular and superior temporal cortex. Importantly, CBF in the dorsal midinsular cortex was both decreased at 1 month postconcussion in slower-to-recovery athletes (t11 = 3.45; P = .005) and was inversely related to the magnitude of initial psychiatric symptoms (Hamilton Depression Scale: r = −0.64, P = .02; Hamilton Anxiety Scale: r = −0.56, P = .046), suggesting a potential prognostic indication for CBF as a biomarker.

CONCLUSIONS AND RELEVANCE To our knowledge, these results provide the first prospective evidence of reduced CBF in human concussion and subsequent recovery. The resolution of CBF abnormalities closely mirrors previous reports from the animal literature and show real-world validity for predicting outcome following concussion.

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most of the 3.8 million sports-related traumatic brain injuries (TBIs) that occur annually are concussions.\textsuperscript{1} Owing to the high incidence and potentially deleterious consequences of repeat injury,\textsuperscript{2,3} it is imperative that methods for accurately and objectively diagnosing the presence and severity of concussions are developed. Reduced cerebral blood flow (CBF) represents one of the most enduring markers of concussion in animal models\textsuperscript{4-6} and is clearly present in studies of more moderate to severe human TBI.\textsuperscript{7-10} However, the use of CBF has not been fully assessed in prospective studies of concussion.

To date, several longitudinal studies have reported disruptions in resting-state and evoked functional magnetic resonance imaging (fMRI) during both the subacute and chronic phases of mild TBI (mTBI).\textsuperscript{11-13} However, the fMRI signal is dependent on changes in cerebral blood volume, the ratio between deoxyhemoglobin and oxyhemoglobin as well as CBF; thus, it is incapable of pinpointing exact mechanisms of underlying pathophysiology following injury.\textsuperscript{14} Other studies specifically examining CBF have suggested that hypoperfusion is present during the chronic phase of mTBI in symptomatic patients.\textsuperscript{15-18} However, chronically symptomatic patients represent the “miserable minority,”\textsuperscript{19} and it may not be appropriate to generalize findings from this cohort to the more typical cases of concussion.\textsuperscript{14} Cross-sectional studies using single-photon emission computed tomography\textsuperscript{20-21} and perfusion computed tomography\textsuperscript{22} have reported reduced CBF during the acute and subacute phases of mTBI. Finally, reduced global CBF has also been reported during the acute phase using arterial spin labeling (ASL) in pediatric mTBI.\textsuperscript{24} To our knowledge, no studies have prospectively examined regional CBF changes during the normal course of recovery that typifies most concussion patients.\textsuperscript{25,26}

Therefore, ASL was collected to measure regional (ie, voxelwise) changes in CBF approximately 1 day, 1 week, and 1 month postinjury in a homogenous sample of male collegiate football athletes. Longitudinal points were selected to mirror the typical recovery period from concussion reported in other large-scale cognitive and behavioral studies,\textsuperscript{25} as well as in the animal literature.\textsuperscript{6} Cross-sectional validation was conducted against healthy football athletes to maximally control for non-specific confounds inherent in the study of National Collegiate Athletic Association athletes (eg, levels of cardiovascular fitness and previous exposure to contact sports). We hypothesized that hypoperfusion would normalize in concussed athletes as they transitioned from the acute to subacute injury phase, and we further predicted that these deficits would relate to real-world measures of outcome and postconcussive symptoms.

Methods

Participants
A total of 44 male student athletes were recruited from a National Collegiate Athletic Association Division I football team. Participants provided written consent and The University of Oklahoma Health Science Center and Western Institutional Review Boards approved all aspects of the study. Seventeen concussed athletes were assessed a mean (SD) of 1.41 (0.94) days postconcussion (T1; range, 0-3 days). Fifteen athletes returned for a second visit a mean (SD) of 8.73 (2.19) days post-concussion (T2; range, 6-13 days), with 13 athletes completing a final assessment approximately 31.46 (4.67) days postconcussion (T3; range, 25-44 days). All concussed athletes completed at least 2 of the 3 visits. Physicians trained in sports medicine diagnosed concussions at the time of injury independently of the study (Appendix 1 in the Supplement). The control group consisted of 27 healthy football athletes. The most recent concussion for athletes in the control group was a mean (SD) of 17.63 (12.41) months prior to scanning date (range, 3-37 months).

Clinical Measures

Structured interviews for the Hamilton Depression (HAM-D)\textsuperscript{27,28} and the Hamilton Anxiety (HAM-A)\textsuperscript{29} rating scales were collected at each visit as primary behavioral measures. The Automated Neuropsychological Assessment Metrics 4 Sports Medicine Battery\textsuperscript{30} provided secondary measures of interest (Appendix 1 in the Supplement). Behavioral scores collected at the initial postconcussion visit (T1) were used to operationalize postconcussion severity. The number of days that athletes were withheld from competition following injury (ie, days until return-to-play decision) was used to stratify groups into good (≤14 days) vs poor (>14 days) outcome using median split. Physicians trained in sports medicine made independent return-to-play decisions based on recommended guidelines.\textsuperscript{31}

Imaging Parameters and Processing

Neuroimaging data were collected using a General Electric Discovery MR750 3-T MRI scanner. Cerebral blood flow data were collected using the General Electric 3dASL sequence and quantified to milliliters per 100 g per minute (Appendix 1 in the Supplement). A relative CBF image was calculated by dividing the smoothed quantified CBF image by the average CBF value.

Statistical Analyses of Behavior

Statistical analyses were performed in Systat. Repeated-measure analyses were performed for each measure using a linear mixed-effects model analysis, with time as a fixed factor and a random intercept to account for missing data. Compound symmetry was selected as the covariance structure. A conservative corrected significance level of \( P < .002 \) was considered following Bonferroni correction for the total number of measures investigated (0.05/23). Pairwise comparisons for measures with a significant main effect of time were considered significant at \( P < .017 \) following additional Bonferroni correction (0.05/3). One-tailed independent-sample \( t \) tests investigated the specific hypothesis that concussed athletes would exhibit more neuropsychiatric symptoms relative to healthy athletes. Supplemental analyses examined the effect of concussion history on CBF and neurobehavioral measures.
statisticaleffectsonCBFandprimarybehavioralmeasuresat
eachpointbetweenathleteswithgoodandpooroutcome,
stratifiedbasedontheindependentjudgmentfromclinical
staff.Effectsizes(δ)arereportedfortheseanalysesgivenlimited
sample size.

Results
There was no significant difference in age (t_{42} = −0.21; P = .84)
or education (t_{42} = −0.95; P = .35) between concussed and
healthy athletes (Table 1). However, there was a trend for con-
cussed athletes to self-report more previously diagnosed con-
cussions than healthy athletes (U = 294.0; P = .08).

Clinical Symptoms and Recovery
The mean, standard deviation, and number of participants for
each behavioral measure are reported in Table 2. Results for Au-
tomated Neuropsychological Assessment Metrics 4 Sports
Medicine Battery measures can be found in eAppendix 2 in the
Supplement. There was a significant main effect of time for both
of our primary outcome measures: HAM-A (F_{2,42} = 20.8; P < .001) and HAM-D (F_{2,42} = 17.4; P < .001). For both mea-
sures, scores were significantly improved at T3 relative to both
T1 (t = 6.4, P < .001 and t = 5.9, P < .001, respectively) and T2
(t = 2.7, P = .01 and t = 3.5, P = .002, respectively) (Figure 1). The
HAM-A scores at T2 were also significantly improved com-
pared with scores at T1 (t = 3.7; P = .001). The HAM-D scores
at T2 were not significantly lower than scores at T1 following mul-
tiple comparison correction (t = 2.3; P = .02). Supplementary
analyses (eAppendices 1 and 2 in the Supplement) indicated no
significant main effect or interaction of prior concussions on
recovery of either the HAM-A or HAM-D scales (P > .10 for all).

Postconcussion scores on the HAM-A were significantly
higher than healthy athletes at T1 (t_{42} = 7.32; P < .001) and
T2 (t_{40} = 5.74; P < .001), and they were trending higher at
T3 (t_{38} = 1.33; P < .10). Postconcussion scores on the HAM-D
were significantly higher than healthy athletes at T1 (t_{42} = 6.77;
P < .001), T2 (t_{40} = 7.30; P < .001), and T3 (t_{38} = 2.38; P = .01).

CBF Differences and Recovery
There was a significant main effect of time in a cluster (4882.4
μL) that included the right superior temporal gyrus and insu-
lar cortex (Figure 2A). The cluster contained 2 peaks in anato-
mically distinct regions located in the right superior tem-
poral sulcus (STS; Montreal Neurological Institute coordinates:
x = 48, y = −10, z = −17) and the right dorsal midinsular cor-
tex (dmIC; Montreal Neurological Institute coordinates: x = 40,
y = −1, y = 11; Figure 2B). For the dmIC peak, post hoc analy-
ses with Bonferroni correction revealed that dmIC CBF was sig-
ificantly lower at T1 (t = −4.50; P < .001; Figure 2C) and T2
(t = −4.19; P < .001) relative to T3. There was no difference in
CBF at T1 compared with T2(t = −0.12; P = .91) within the dmIC.
The results for the STS peak were similar, with CBF signifi-
cantly lower at T1 (t = −3.75; P < .001) and at T2 (t = −4.77;
P < .001) relative to T3, and no difference between T1 and T2
CBF (t = 1.26; P = .22). Supplemental analyses indicated no sig-
nificant main effect or interaction of prior concussions on CBF

Table 1. Player Position, Medication Status, and Demographic Information

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<th>Characteristic</th>
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<th>Healthy</th>
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Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

* T1 indicates 1 day; T2, 1 week; and T3, 1 month postinjury.

** The same healthy athlete.

† One concussed athlete reported both posttraumatic and retrograde amnesia.

Statistical Analyses of CBF
An identical voxelwise linear mixed-effects model assessed
changes in CBF as a function of recovery in the concussed
athletes. To avoid thresholding effects, post hoc analyses
were performed on the average CBF from spherical (radius = 5 mm)
regions of interest created at peak voxels exhibiting signifi-
cant main effects of time (highest F value). Pairwise compar-
sions were considered significant at P < .017 following Bonfer-
noni correction (0.05/3).

To confirm that regions showing a significant effect of time
represented reduced CBF, peak region of interest data from the
concussed participants were directly compared with healthy
athletes using 1-tailed independent-sample t tests (P < .05). Fi-
nally, 2-tailed independent-sample t tests were used to com-
pare postconcussion CBF and primary behavioral measures at
each point between athletes with good and poor outcome,
stratified based on the independent judgment from clinical
staff. Effect sizes (δ) are reported for these analyses given lim-
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CBF (t = 1.26; P = .22). Supplemental analyses indicated no sig-
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Figure 1
recovery for the dmIC or STS (P > .10; eAppendices 1 and 2 in the Supplement).

Concussed data from the right STS and dmIC CBF were next compared with that of nonconcussed football athletes. The results indicated significant differences in right dmIC CBF in concussed athletes relative to control athletes at T1 (t_{42} = −1.73; P = .046; Figure 2C) and T2 (t_{40} = −1.77; P = .04), with nonsignificant differences at T3 (t_{38} = 1.09; P = .86). Similarly, CBF in

### Table 2. Supplementary Clinical Measures

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<td>Mean (SD) No.</td>
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</table>

Abbreviations: CSI, Concussion Symptom Inventory; math, mathematical; OSI, Overall Symptom Inventory; RT, reaction time; subs, substitution.

* T1 indicates 1 day; T2, 1 week; and T3, 1 month postinjury.

### Figure 1. Recovery of Primary Behavioral Measures

A. Hamilton Anxiety Rating Scale

B. Hamilton Depression Rating Scale

Scatterplots are displayed for the Hamilton Anxiety Rating Scale (A) and Hamilton Depression Rating Scale (B), representing the primary behavioral variables of interest. Data are presented for healthy athletes (open circles) and concussed athletes (filled circles) at the 3 postinjury points (T1 = 1 day; T2 = 1 week; and T3 = 1 month).
the right STS was also reduced at T1 ($t_{42} = -3.06; P = .002$) and T2 ($t_{40} = -3.98; P < .001$) for concussed athletes relative to control athletes, with a return to normal levels at T3 ($t_{38} = 0.46; P = .68$).

**Relationship Between Outcome and Other Variables**

There were no differences in dmlC CBF at T1 ($t_{15} = 1.22; P = .24; d = 0.60$) or T2 ($t_{13} = 0.40; P = .70; d = 0.21$) in athletes with poor outcome compared with athletes with good outcome (Figure 3A). However, concussed athletes with poor outcome had significantly lower dmlC CBF at T3 relative to those with good outcome ($t_{13} = 3.45; P = .005; d = 1.92$). For the STS region of interest, there were no differences in CBF between athletes with poor and good outcomes at T1 ($t_{15} = 0.65; P = .52; d = 0.32$), T2 ($t_{13} = -1.70; P = .11; d = -0.90$), or T3 ($t_{11} = 0.62; P = .55; d = 0.34$). Although only significant at the first visit, total scores on the primary behavioral measures (HAM-A and HAM-D) were higher (ie, more severe) for the poor outcome group compared with the good outcome group at each visit, with moderate to large effect sizes (T1: $t_{15} = -2.9, P = .01, d = -1.40$ and $t_{13} = -2.62, P = .02, d = -1.27$, respectively; T2: $t_{13} = -1.79, P < .10, d = -0.94$ and $t_{13} = -1.34, P = .20, d = -0.71$, respectively; and T3: $t_{11} = -1.19, P = .26, d = -0.66$ and $t_{11} = -1.65, P = .13, d = -0.92$).

Exploratory analyses (uncorrected at $P < .05$) were performed to assess the relationship between T1 clinical mea-
suresshowingasignificantimprovementovertimewithdmIC CBF at T3 based on the relationship with outcome. The re-
sults indicated an inverse relationship between dmIC CBF at
T3 and initial concussion severity as measured by our pri-
mary measures of postconcussive symptoms (HAM-D:
\(r = -0.64, P = .02\) and HAM-A: \(r = -0.56, P = .046;\) Figure 3B).
Correlations with other behavioral measures exhibiting a main
effect of time were not significant \((P > .10 \text{ for all})\).

Discussion

To our knowledge, this is the first study to longitudinally
investigate changes in regional CBF from the acute through
subacute phases of concussion. In a homogenous sample of
collegiate athletes, we observed decreased CBF in the right
dmIC and STS during the first week postinjury, which
showed longitudinal evidence of recovery at 1 month
postinjury. Cerebral blood flow in these regions was also sig-
ificantly reduced at 1 day and 1 week postinjury compared
with a cohort of healthy football athletes, with no differ-
ences between groups at 1 month postinjury. Importantly,
our selection of carefully matched collegiate football ath-
estes avoids the potential confounds of sex and age, as well
as potential confounds of exercise-induced cardiovascular
changes that have affected other studies of concussion.
Cerebral blood flow in the dmIC at 1 month was inversely
associated with both concussion severity and independent
assessment of outcome in concussed athletes. Thus, the
current results suggest that regional CBF may provide an
objective biomarker for tracking both normal and poten-
tially pathological recovery from concussion.
Significant cross-sectional and longitudinal evidence of recovery was observed for our primary neuropsychiatric measures of depression and anxiety. In addition, athletes with poor outcome as determined by our independent real-world measure had more severe depression and anxiety scores at each point, all of which would have likely been significant with a larger sample size. Significant evidence of recovery was also observed across several cognitive and self-report measures commonly used in sports medicine concussion batteries. Specifically, cognitive and neurobehavioral measures from the Automated Neuropsychological Assessment Metrics 4 Sports Medicine Battery indicated a statistical recovery from concussion symptoms within 1 week of injury, a finding that is consistent with previous large-scale clinical studies demonstrating that most patients (80%-95%) report recovery within 7 to 10 days.25,26

Interestingly, a slightly delayed recovery curve was observed for the 2 structured interviews for depression and anxiety, which could have resulted from several factors. First, temporal differences in the resolution of self-reported vs assessed psychiatric sequelae may have resulted from an expert and independent evaluation vs potentially biased self-report motivated by a desire for more rapid return to play.34,35 Second, it is possible that the emotional symptoms of concussion may have a slower course of recovery than cognitive and somatic symptoms typically measured in self-report.39 Alternatively, current results could be reflective of clinician rater bias (ie, nonblinded) in the assessment of postconcussive symptoms.

Observation of reduced cerebral perfusion following sports-related concussion is consistent with both animal models of TBI4–6 as well as cross-sectional studies of acute/subacute21–24 and chronically symptomatic15–18 mTBI patients. However, we were unable to delineate whether the observed CBF changes were a direct result of the primary injury or secondary to other factors. Previous fluid percussion injury studies in rodents have indicated both a semiacute reduction in capillary number and diameter at the injury site as well as distally,37 suggesting that the structural integrity of the microvasculature may directly contribute to reduced CBF. Similarly, hemosiderin depositions secondary to microhemorrhages and inflammation have been noted in human cases of mTBI using both noninvasive neuroimaging and at autopsy.38 Changes in the autoregulation of perfusion have also been documented post-mTBI, providing an alternative mechanism for explaining our findings of reduced CBF.39 Finally, animal models suggest a decoupling between CBF and the oxidative metabolism of glucose, both of which remain affected longer than most other markers of injury.6 Multimodal imaging studies are needed to pinpoint the mechanisms behind CBF alterations in mTBI.

Although evidence of CBF recovery was observed in both the STS and dmIC, only CBF in the dmIC was inversely associated with an independently obtained measure of concussion outcome and initial symptom severity. The dmIC belongs to a middle-posterior insular network that has been associated with visceral (ie, autonomic) input (eg, pain) plays a role as a general salience and action system and participates in functions of body orientation and response selection.40–42 Common concussion symptoms, including balance problems, dizziness, and reduced reaction times,31 could possibly be related to the disruption of this network.

The current findings have important implications for the management of concussion. Return-to-play decisions are currently based on clinical judgment that is informed by neurocognitive batteries and self-report symptom metrics rather than on evidence-based biomarkers. Although evidence suggests that other physiological consequences of concussion might extend beyond typical symptom resolution,13 these results suggest a potential temporal relationship between the timeframe of CBF recovery and the resolution of symptoms previously reported in other large-scale clinical studies.25,26 Moreover, the impaired recovery of dmiC CBF at 1 month post-concussion was also related to symptoms of anxiety and depression, suggesting a potential relationship between CBF-based recovery and the initial neurobehavioral symptoms. Finally, although no effect of prior concussions was observed on the recovery of CBF or behavioral measures, previous large-scale studies have suggested that a history of concussion presents a risk factor for slower recovery time.43 Thus, the relationship between previous concussions on CBF recovery requires additional research.

Future studies identifying the time course of metabolic dysfunction following concussion and its relationship to CBF are crucial to characterize the physiological effects of concussion. Specifically, the cerebral metabolic rate of glucose, the cerebral metabolic rate of oxygen, and CBF are tightly coupled in health44 but become dysregulated following mTBI.6 Additionally, a reduction in the ratios of N-acetylaspartate to creatine and choline is pronounced at 3 days postconcussion but fully recovered by 1 month.45 In preclinical studies, subsequent injuries prior to metabolic recovery lead to intensified metabolic and behavioral consequences,46–48 which may be more preventable with objective biomarkers. Additionally, although the precise etiology of second-impact syndrome remains controversial and the incidence is rare, it is postulated to result from autodysregulation of intracranial and cerebral perfusion pressures following concussion.49 The development of objective biomarkers to measure CBF recovery after concussion may have clinical use for reducing the incidence of this rare but fatal disorder.

The current results also make several other important contributions to the existing literature. First, we used a voxel-wise analysis to pinpoint the location of CBF abnormalities and subsequent recovery rather than relying on global CBF measures as has been done previously.24 The study of regional rather than global measures of CBF becomes even more critical for future attempts to quantify subject-specific abnormalities in flow, as has been done previously using other imaging modalities.50 Second, the current findings also have implications for studies that use blood oxygen level-dependent imaging to delineate the neurophysiology of concussion and mTBI such as task-evoked and resting-state fMRI.51 Specifically, differences in the blood oxygen level-dependent signal in populations with altered CBF might reflect perfusion rather than neuronal differences. Future studies examining ASL perfusion and blood oxygen level-dependent fMRI simultane-
Cerebral Blood Flow Following Sports-Related Concussion

Original Investigation Research

Conclusions

To our knowledge, this study provides the first prospective evidence of reduced CBF and subsequent recovery following concussion in a homogenous sample of collegiate football athletes and also demonstrates the potential of quantified CBF as an objective biomarker for concussion. These data demonstrate that the acute and subacute phases of sports-related concussion are associated with perfusion deficits that show both longitudinal and cross-sectional evidence of recovery. The current findings mirror previous results from the animal literature and show real-world validity for predicting outcome following concussion.

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