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Project Title: The role of brain magnetic resonance imaging in pediatric sports-related concussion

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SUMMARY: (no more than 250 words single spaced)

The present study utilizes brain magnetic resonance imaging protocols in various forms to investigate it's utility in the management and understanding of concussion. In the first phase of this study, neuroimaging findings from an adolescent sport-related concussion (SRC) cohort are summarized. The current guidelines for neuroimaging use have never summarized findings from this particular group and thus it was important to rule out the presence of structural abnormalities following an SRC.

In the second phase of the study, we administered an MRI CO2 brain stress test to patients with post-concussion syndrome (PCS) and a group of age matched controls. Using two MRI protocols, blood-oxygen level dependent (BOLD) and pseudo-continuous arterial spin labelling (pCASL), we were able to examine the cerebrovascular responsiveness (CVR) to the vasoactive CO2 stimulus. The CO2 stimulus was administered using model-based prospective end-tidal (MPET) CO2 targeting delivered from a computerized gas-blender.

Significantly findings from the study indicate that PCS may be characterized by patient specific alterations in regional blood flow and CVR despite normal global mean resting cerebral blood flow. Further work with this technology may be able to provide insights into the physiology of PCS as well as acute SRC.

Student Signature

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The role of brain magnetic resonance imaging in pediatric sports-related concussion

Introduction and Background

Sports-related concussion (SRC) is a significant problem affecting thousands of adolescents in Canada and United States each year.(1) As a form of mild traumatic brain injury (mTBI), patients with SRC may experience a range of physical, cognitive, sleep and affective symptomatology. The majority of these patients will experience spontaneous recovery within 1-4 weeks, however, an estimated 15-20% will develop post-concussion syndrome (PCS), a condition characterized by symptoms lasting for greater than 1-3 months.(2)(3) The current mainstay of treatment for SRC and PCS is a period of physical and cognitive rest followed by gradual reintegration to sports and scholastic activities. At present there are few clinical tools capable of quantifying the degree of injury or more importantly the degree of recovery achieved in acute SRC and PCS patients.

Experimental animal studies have suggested that acute concussions are characterized by a constellation of physiological changes including altered neural activity, astrocyte function, excitatory neurotransmitter release, cellular metabolism and cerebral blood flow (CBF).(4,5) Despite this experimental insight, there are limited objective assessment tools that provide a window into the structural and functional consequences of SRC and PCS.

Phase 1: A retrospective study to summarize the results of clinical neuroimaging performed in adolescent SRC patients.

Traditionally, based on findings described above, neuroimaging has been determined to be non-contributory in the management and diagnosis of SRC and mTBI. At present, numerous published position statements recommend neuroimaging be utilized only when there is a concern regarding serious intracranial pathology such as subdural, epidural and intraparenchymal hemorrhage or in patients with prolonged disturbed level of consciousness, focal neurological defects or worsening symptoms. (6)(7) Despite the consistency of these statements, these guidelines are based on expert opinion (Level 5 evidence) and to date, no studies have been undertaken to summarize the neuroimaging findings in an exclusive pediatric SRC cohort.

In recent years, advanced imaging techniques with MRI, such as susceptibility weighted imaging (SWI) and gradient echo (GRE) have helped to improve detection of functional changes in head injuries. These two sequences are both very sensitive to the magnetic properties of blood and have permitted increased detection of diffuse axonal injury (DAI) as well as cerebral micro-hemorrhages in pediatric TBI populations.(8)(9) Preliminary studies using these techniques have failed to show changes in the mTBI and SRC populations, however, as study designs often included patients with no clinically defined indication for neuroimaging. The retrospective phase of this study sought to summarize findings from neuroimaging studies performed in patients with adolescent SRC.

Because SRC is conceptually viewed as a functional rather than a structural brain injury, we sought to develop a technique that would allow us to quantify the functional changes that underlie PCS and potentially acute SRC.

Phase 2: Prospective study examining the qualitative and quantitative changes in cerebrovascular responsiveness during MRI CO_2 stress testing in adolescent PCS patients and healthy age-matched control subjects.

Several studies have attempted to examine the functional changes using sophisticated neuroimaging techniques including magnetoencephalography, diffusion tensor imaging and task-based functional MRI.(9)(10) Despite the fact that differences between healthy controls and concussion patients were demonstrated, no singular technique emerged as a useful clinical tool. As such, there remains an urgent and unmet need for a neuroimaging assessment technique capable of reliably detecting the alterations in brain physiology associated with acute SRC and PCS.

One of the physiological parameters, CBF, is regulated by a number of factors including arterial partial pressure of carbon dioxide ($PaCO_2$). $PaCO_2$ is the most potent stimulus of arterial dilatation whereby each 1 mmHg elevation in $PaCO_2$ corresponds to a 2-15% increase in CBF.(11,12) Cerebrovascular reactivity or responsiveness (CVR) is defined as the change in CBF in response to a vasoactive stimulus. Previous research on TBI has shown that impaired CVR in response to a CO_2 stimulus is an independent risk factor for poor outcomes and death in severe pediatric TBI. (13)

To examine this relationship in concussion patients, a pilot study from our group introduced a novel MRI brain stress test utilizing blood oxygen level-dependent (BOLD) MRI during model-based prospective end-tidal (MPET) CO_2 targeting.(14) We were able to demonstrate qualitative global and regional CVR alterations present in adult PCS patients compared to healthy matched controls. Additionally a quantitative biomarker, expressed as abnormal voxel counts, was observed to be significant in PCS patients compared to controls. Phase 2 of this study will provide results from BOLD and pseudo-continuous arterial spin labeling (pCASL) analysis in a cohort of pediatric patients with PCS secondary to a SRC.

Materials and Methods

Research Design

Phase 1: Single-center, retrospective review of medical charts and neuroimaging reports for patients referred to the Pan Am Concussion Program (PACP) at Pan Am Clinic in Winnipeg, Manitoba from September 1st, 2013 to July 31st, 2014. Patients were referred from various family doctors, emergency departments, athletic therapists and coaches. Inclusion criteria included: 1.) age ≤ 19 years of age, 2.) neurosurgeon-diagnosed SRC. Exclusion criteria included: 1.) diagnosed concussion occurring outside of a sporting activity, 2.) incomplete medical records, 3.) neuroimaging studies that were undertaken as a part of research studies. Concussions sustained during non-specific gym class and schoolyard activities were excluded.

Phase 2: Prospective cohort study of adolescent PCS patients and healthy controls. All PCS patients were recruited from the Pan Am Concussion Program. Patient inclusion criteria included: 1) physician- diagnosis of PCS secondary to a SRC (defined as meeting the *ICD-10* criteria of 3 or more concussion symptoms present for at least 1 month)(15); 2) age 13 – 25 years. Patient exclusion criteria were: 1) the presence of traumatic abnormalities on prior neuroimaging studies; 2) diagnosis of PCS following a concussion outside of sports; 3) contra-indication to MRI (i.e claustrophobia). Healthy control subjects were recruited through word of mouth including patient siblings and relatives. Control subject inclusion criteria included: 1) age 25 or younger. Control subject exclusion criteria were: 1) the presence of a symptomatic

concussion; 2) history of prior concussion or TBI resulting in structural brain injury on previous neuroimaging; 3) contra-indication to MRI.

Clinical Assessment

All patients underwent a clinical assessment by a single neurosurgeon. In phase one, patients were diagnosed with a SRC according to the International Consensus on Concussion in Sport.(6)It was not possible to confirm the diagnostic criteria used for the initial diagnosis of concussion prior to referral to the PACP. Additionally, the specific indications for clinical neuroimaging were absent. In phase 2, patients were diagnosed with PCS according to ICD-10 criteria. Demographic, past medical history and past concussion history was collected for all patients. On the day of imaging, all patients completed a Post-Concussion Symptom Scale (PCSS), which is a standardized symptom inventory with 22 symptoms each being ranked on a 7 point (0-6) Likert scale.

Assessments

Phase 1: Neuroimaging was completed at multiple hospitals using CT and MRI scanners. All CT scans were non-contrast studies. MRI protocols differed across the various sites and are summarized in Table 1.

Phase 2: Model-based prospective end-tidal (MPET) CO_2 targeting was achieved by precise delivery of CO_2 at a fixed concentration using a re-breathing circuit regulated by a computerized gas-blender (RespirAct, Thornhill Research Inc, Toronto, ON). This device allows precise manipulation of $ETCO_2$ levels under isoxic (target ETO_2=115 mmHg) conditions. (16) Monitoring during the study period included continuous heart rate and pulse oximetry and non-invasive blood pressure (BP) at 3-minute intervals.

All images were acquired using a Siemens Verio 3.0T MR scanner with a 12-channel phased-array head coil. The MR-imaging protocol consisted of baseline anatomical imaging including sagittal 3D T1 MPRAGE (whole brain coverage; matrix: 256×256; slice thickness: 2.2 mm; no interslice gap), axial fluid-attenuated inversion recovery (FLAIR) and axial gradient recalled echo planar (GRE) sequences with no MPET targeting followed by a run of continuous BOLD and pseudo continuous arterial spin labeling (pCASL) imaging while the patient underwent a provocative breathing sequence.

The breathing sequence during BOLD imaging consisted of interval step-changes as follows: baseline $ETCO^2$ (120 seconds), hypercapnia (5 mmHg above baseline for 120 seconds), baseline $ETCO_2$ (30 seconds), hypercapnia (5 mmHg above baseline for 120 seconds), baseline $ETCO_2$ (30 seconds), hypercapnia (5 mmHg above baseline for 120 seconds), baseline $ETCO_2$ (120 seconds – see Figure 2). BOLD MRI data was acquired with a T2*-weighted single-shot gradient echo pulse sequence with echoplanar readout (field of view: 24×24 cm; matrix: 64×64; TR: 2000 ms; TE: 30 ms; flip angle: 85°; slice thickness: 5.0 mm; interslice gap: 2.0 mm; number of temporal frames=330). The total duration of the MRI assessment was approximately 25 minutes.

The breathing protocol used for pCASL imaging was 3 minutes of breathing at the subject's baseline (BL) end-tidal CO_2 followed by a step change whereby the end-tidal CO_2 was increased by 5 mm Hg (hypercapnia) for a further 3 minutes (see Figure 3).

An M0 scan was undertaken first - Siemens ep2d_pCASL – echo planar readout (field of view 24 × 24 cm, TR 8000 ms, TE 12 ms, contrast with a flip angle 90°, 20 slices, CASL method – multislice, label offset 90 mm, post label delay 1200 ms, crusher gradient 0 s/mm^2; voxel size 3.8 × 3.8 × 5.0 mm. Then the formal pCASL sequence: echo planar readout (field of view 24 × 24 cm, TR 4000 ms, TE 12 ms, contrast with a flip angle 90°, 20 slices, slice thickness 5.0 mm, CASL method – multislice, label offset 90 mm, post label delay 1200 ms, crusher gradient 0 s/mm^2; voxel size 3.8 × 3.8 × 5.0 mm. The first two labeled, non-labeled pairs were discarded. There were 22 pairs for the baseline CBF determination and 22 pairs for the hypercapnic determination.

Non-invasive continuous hemodynamic monitoring of heart rate (HR) and pulse oximetry was performed while blood pressure (BP) was monitored in roughly 3 min intervals.

Statistical Analysis

Phase 1: Outcomes examined were frequency of neuro-imaging studies performed and the findings of those studies. Descriptive statistics were used to summarize. The statistical analyses was performed using SPSS 22.0 (IBM Corp. Armonk, NY, USA)

Phase 2: *Structural neuroimaging* – all scans were evaluated by a board-certified neuro-radiologist.

Preprocessing of MRI sequences: Statistical Parametic Mapping 8 (SPM8) software was used for preprocessing utilizing custom Matlab scripts. Voxel size was reported as 2x2x2 mm. The preprocessing sequence involved image re-alignment, slice time corrections, co-registration with MPRAGE images, smoothing and normalization into MNI space. Motion artifact was examined and dealt with accordingly. Studies were rejected in motion was greater than 3 mm in any plane.

First Level Analysis:

BOLD - the activation response to the hypercapnic stimulus was evaluated for each patient. The inverse response was also assessed, both were at p=0.001 uncorrected level. The cluster size threshold was 10 voxels.

pCASL – Mean CBF at baseline and hypercapnia were calculated on a voxel-by-voxel basis and reported as the global mean CBF. Regional differences were also directly compared on the flow maps. CVR was then calculated based on the delta flow signal (hypercapnia flow maps – baseline flow maps). Flow maps were normalized by dividing each voxel output by the individual CO_2 delta that was actually achieved (mean hypercapnic CO_2 – mean BL CO_2).

Second Level Analysis:

BOLD – all control patients (n=17) were combined into an atlas forming a ‘normal’ response. Each PCS patient and control was then able to be compared to this atlas of control means. Comparisons of voxel counts that were less than or greater than the mean control group were completed over a range of p-values (p=0.001, 0.005, 0.01 and 0.05).

pCASL – a healthy control subject atlas (n=15) was created. The mean CBF from the PCS group was then compared to the mean of the control group (n=15). Additionally, each individual subject was compared to the control atlas at p-values of p=0.001, 0.005, 0.01 and 0.05). Results were reported for two conditions: greater than regional CBF and less than CBF compared to the control atlas. In addition to regional CBF analysis, the

same analysis was used to examine the CVR

Receiver Operating Characteristic (ROC) Analysis: predictive accuracy is defined as the ability of a test to identify whether or not a patient has a specific condition. When applying area under the curve (AUC) to an ROC analysis, perfect discrimination is equal to 1.0 while ROC curve of $\geq$ 0.70 is considered a clinically useful test. In this case, we examined whether the novel biomarker, *abnormal voxel count,* could discriminate healthy controls (0) from patients with PCS (1). For both BOLD and pCASL sequences, an ROC analysis was completed. Curves were generated based on voxel counts determined for each patient across the range of p-values described.

Results

Phase 1:

During the study period, 151 (65 male, 86 female) were diagnosed with SRC and referred to the Pan Am Concussion program. The mean age was 14.26 +/- 2.21 years (range 5-19). 24/151 (16%) underwent CT-imaging, of which 19/24 (79%) were completely normal. Abnormal results included calvarial skull fracture (n=1), orbital floor fracture (n=1), posterior fossa arachnoid cyst (n=1), focal hyperdensity suspicious of hemorrhage in basal ganglia (n=1), and an isodense left sylvian fissure lesion suspicious for hemorrhage into small sylvian fissure arachnoid cyst (n=1).

16/151 (11%) of patients underwent MRI imaging, including 4 who had already had a CT scan. All MRI were outpatient and referred from the PACP except for 1. The clinical indications for MRI were, persistent symptoms (n=12), focal neurological defect (n=1), abnormal CT findings (n=2) and constitutional symptoms (n=1). 12/16 (75%) had normal MRI sequences. Abnormal findings included intraparenchymal hemorrhage and a sylvian fissure arachnoid cyst (n=1), non-hemorrhagic contusion (n=1), multi-focal demyelinating disease (n=1), and a posterior fossa arachnoid cyst with non-specific white matter changes (n=1). A summary of MRI findings is presented in Table 1. Representative images from patients with traumatic abnormalities detected on MRI are shown in Figure 1.

Phase 2:

Participants: a total of 37 subjects were enrolled in the imaging study. For the BOLD analysis, 32 subjects are included in the analysis (17 controls and 15 PCS). The control group consisted of 8 males and 9 females while the PCS group was 4 males and 11 females. In the pCASL analysis, 30 subjects are included (15 control, 15 PCS). The discrepancy of subjects in the control group during the pCASL analysis was due to the exclusion of 2 female subjects for excessive movement during imaging. Other causes of exclusion were – 1 subject with dental braces causing serious image degradation, 2 subjects whose CO_2 targeting failed due to improper mask seal and 2 subjects due to MPET equipment failure. The study was well tolerated by all subjects and there were no abnormal findings on structural neuroimaging. The end-tidal gas targeting values were recorded and are reported in Table 2. There were no differences between the magnitude of CO_2 stimulus between groups.

First Level Analysis:

BOLD – at the p=0.001 level there was no significant difference between groups for activation (or inverse) to the CO_2 stimulus. The mean activation was 64 +/- 22% for PCS and 67 +/- 17% for control subjects (p=0.56 between groups). The inverse response was 0.37 +/- 0.26% in the PCS group and 0.24% +/- 0.22% in controls (p=0.35).

pCASL – there were no differences in mean global CBF between controls and PCS patients. There were modest significant differences in regional mean baseline CBF in the 2nd level analysis at the p=0.01 level. (Figure 4) A similar modest difference was observed for the CVR analysis at p=0.01 (Figure 5)

Second Level Analysis:

BOLD – voxel-by-voxel comparisons of mean value for the control group compared to the PCS group is presented in Figure 6. Only 0.15% of voxels were significantly greater in the PCS group compared to 5.8% that were significantly less when compared to controls. Patient specific alterations were observed on the individual comparisons of PCS patients to the control atlas that were not detected in the group analyses.

pCASL - Individual comparisons of PCS subjects compared to the control group atlas demonstrate patient specific CBF differences (Figure 5 - B and C). Similarly, regional individual CVR differences for the PCS subjects were noted have significant alterations when compared to the group atlas.

ROC Curve Analyses:

BOLD – this was undertaken at all 4 p-values and used to compare each individual subject, both controls and PCS, to the control atlas. The ROC curve for regions with a greater than response or less than response for p=0.001 are shown in Figure 7A and B respectively. The AUC is 0.87 for the greater than condition and 0.80 for the less than condition. A multivariate logistic comparison was also undertaken based on various p-value voxels outputs for both greater than and less than outputs. In this model, the ROC AUC = 0.967.

pCASL – the AUC results for ROC analyses at various p-values for greater than and less than CBF voxel counts are presented in Table 3. CVR ROC analysis results are presented in Table 4 for the range of p-values tested. In general, the CVR analysis resulted in greater AUC values than the baseline CBF values. In the case of CVR, a multivariate analysis including both greater than and less than values was a superior test as it increased the AUC to 0.88 ($p<0.0001$ likelihood predictor)

Discussion

Phase 1 of this study provides empirical evidence that the majority (78%) of adolescents with SRC have normal findings on structural neuroimaging. Overall, we found that 21% of patients who underwent CT-imaging had abnormal structural findings. Given that these patients were referred to imaging based on the clinical experience of the emergency room physician, our findings are consistent with the literature stating that the vast majority of adolescent SRC and mTBI imaging studies are normal.(8,17) Due to the risk of radiation exposure in the young population, the use of CT-scans should follow evidence-based clinical prediction rules and be reserved for ruling out intracranial hemorrhage or skull fractures in this population(18). With regards to the use of MRI imaging, numerous studies have stated that imaging is normal in the vast majority of cases for pediatric SRC and mTBI(19,20). However, given the lack of indication for pursuing an MRI, these studies appear to have recruited a convenience sample of subjects and thus must be questioned. In this study, abnormal findings were present in 25% of patients who were referred as outpatients for an MRI scan. In 3 cases, structural abnormalities were detected that directly impacted clinical decisions including return-to-sport. These cases support the need to consider use of MRI when clinical indications such as focal neurological defects, worsening/worrisome symptoms or inconclusive CT scans are present.

The findings from phase 1 must be considered in light of several limitations. First, the patients referred to the PACP may represent a population of patients with more severe injuries and thus would be more likely to have abnormalities on structural imaging. Second, due to the nature of CT scans occurring in the emergency setting, it was not possible to determine the clinical indications for imaging to be performed. Third, the clinical decision making guidelines for referral to MRI were not based on strict guidelines but rather were based on the clinical expertise of the treating neurosurgeon. Due to these selection biases, it is not possible to extrapolate these results to a general population of adolescent SRC patients. To address these issues, a future prospective study will be completed by our research group during which imaging protocols and indications will be standardized.

During phase 2, we were able to empirically determine that adolescent PCS is characterized by alterations in CVR to a controlled CO_2 stimulus that are not present in the control subjects. This study, to our knowledge, is the first study to examine global resting CBF, regional mean resting CBF, and CVR in adolescent PCS patients. The findings suggest that patient-specific regional impairments of mean resting CBF and CVR occur in spite of normal global resting CBF values in adolescent PCS.

At present, little is known of the exact physiological mechanisms that characterize acute SRC and PCS. Experimental animal studies suggest that impairments in neuronal activation, cellular metabolism and regulation of CBF can contribute to the presence of symptoms in the acute setting.(4,5) Whether or not this neurometabolic cascade is responsible for the persistence of symptoms in PCS is not yet known. Intact CVR is important to help maintain CBF during states of rest, exercise, and disease. In cases where CVR is impaired or exhausted due to injury, regional CBF may be adversely affected to the point of symptoms occurring at rest or during increased physiological stress (i.e. hypercapnia, exercise). The use of non-invasive MRI protocols such as ASL, pulsed ASL or pCASL, has allowed a multitude of studies to examine CBF in patients with stroke, TBI, and mTBI.

Among these, Maugans et al.(19) examined CBF in 12 adolescents during the acute phase SRC and during their recovery; concussion subjects were compared against age- and gender-matched controls. With the use of ASL MRI, they determined that during the acute phase of SRC, patients have significantly altered, most often reduced, resting CBF. Meier et al.(21) analyzed the mean resting CBF in a prospective trial involving 17 collegiate football players with SRC and 27 healthy football athletes. They assessed relative mean CBF within selected regions of interest and found alterations in the dorsal midinsular cortex (dmIC) and superior temporal sulcus (STS) present only in the SRC group. Most importantly, in a longitudinal assessment of the SRC subjects, the deficits were lower at one day post-injury than at one month post-injury suggesting there may have been a recovery from injury.

The findings from our study contribute novel findings to the understanding of the physiological events involved in adolescent PCS. First, we determined that mean resting CBF is normal in PCS subjects when compared to controls. These findings come from a sample of subjects of which the majority were diagnosed with physiologic post-concussion disorder – a symptom limited threshold during a graded exercise protocol. The normal resting values considered in isolation may suggest recovery of normal brain physiology, however, the fact that these patients also have exercise induced symptom exacerbation suggests that resting global mean CBF is not a good marker of recovery and thus should not be considered a reliable biomarker for this population.

Second, the present study demonstrates that adolescent PCS is characterized by patient-specific alterations in resting regional CBF and CVR. These findings are consistent with the literature in that the predominant response observed in the PCS group was an attenuated CVR response to the CO_2 stimulus.(14,22) In the second level voxel-by-voxel analysis, each PCS patient expressed a patient-specific pattern of impaired response that was not observed in

the healthy control group, these findings were present during both the BOLD and pCASL sequences. One of the significant findings from the BOLD analysis comes from the ROC analysis related to the quantitative biomarker *abnormal voxel counts.* The AUC values of 0.87 ($p<0.0001$), and 0.80 ($p<0.0001$) for less than and greater than responses, respectively, suggest that further work is indicated. In the pCASL analysis, a multivariate ROC analysis yielded an AUC of 0.88 ($p<0.0001$). Ultimately, both sequences show promise and may be helpful for the diagnosis of PCS as well as in determining physiologic recovery.

The findings of this study also warrant the investigation into CBF and CVR of adolescent acute SRC. Studies involving this unique population will be possible because this preliminary study has proven that the MPET CO_2 stress test and MRI sequences are well tolerated and safe. There is no radiation or contrast administered, no patient voluntarily withdrew and only 2 patients experienced mild worsening of symptoms that were self-limited. Additionally, the MPET CO_2 stimulus used in this study proved to be reliable and reproducible for quantitative (voxels) and qualitative (color maps) assessments of cerebrovascular physiology.

The MPET CO_2 stimulus improves on many of the shortcoming of previous CVR studies. Importantly it does not rely on breath holding or administering acetazolamide which has been found to be unreliable and commonly exacerbates symptoms in adolescent SRC patients.(23) Furthermore, due to the nature of the whole brain stimulus, there is no need to attempt to correlate regional patterns with specific brain topography as is the case with fMRI studies.(24) Finally, this technique is a passive process which removes patient effort from the equation which becomes important in athletes who may wish to return to sport ahead of complete recovery.(25)

The findings of this study must be considered in light of several limitations. First, the sample size is quite modest and includes a sample of PCS patients with a wide range of symptoms and symptom acuity. Secondly, the analysis of a BOLD MRI sequence can be influenced by a number of factors such as blood volume, deoxy- and oxyhemoglobin ratios, local diffusion effects as well as regional CBF.(21) Therefore BOLD MRI does not provide a direct measure of CBF and thus with regards to the BOLD imaging, CVR is more appropriately represented by the term *cerebrovascular responsiveness,* a change in BOLD signal per unit change in CO_2, rather than cerebrovascular reactivity. The pCASL sequence on the other hand, addresses these concerns and is considered a direct measurement of CBF, and therefore CVR. However, the image resolution in the pCASL sequence is inferior and the signal is often considered noisier. These limitations highlight the need for continued work with CO_2 stress testing as imaging sequences and quality improve.

Acknowledging these procedural and methodological concerns, this study is the first to examine the cerebrovascular responsiveness (BOLD CVR) and global resting CBF using a controlled CO_2 stimulus. There is empirical evidence to show that alterations in CBF and CVR are present in adolescent PCS and can be reliable detected through the use of MRI CO_2 stress testing. Future studies are warranted to aid in the diagnosis, longitudinal assessment and management of acute pediatric SRC and PCS.

In conclusion, our study demonstrates that Structural neuroimaging is normal in the vast majority of pediatric SRC patients, but in selected cases can provide information that impacts clinical decision-making. Furthermore, MRI brain CO2 stress testing demonstrates that adolescent PCS is characterized by patient specific alterations in regional resting CBF and CVR in the setting of normal global resting mean CBF. Further studies are needed to optimize the use of structural and MRI brain CO2 stress testing in children with acute SRC.

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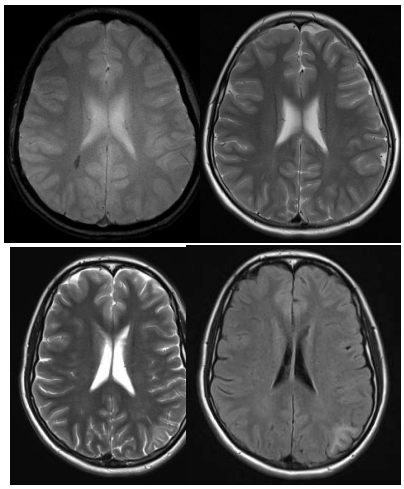
Figure 1.

A.) B.)



Case #1: 11 year old male sustained a concussion during a hockey game. Axial gradient echo image (A) demonstrates curvilinear hypointensity consistent with right occipital intraparenchymal hemorrhage that was not visualized on axial T2-weighted imaging (B). Based on the neuro-imaging findings, we advised the parents that the child should not return to contact sports.

Case #2: 14 year old female sustained a concussion during a ringette game. Axial T2-weighted (A) and fluid attenuated inversion recovery (B) imaging demonstrates evidence of left parietal non-hemorrhagic contusion. Based on concordant neuropsychological testing and neuro-imaging findings, we advised the parents that the child should not return to contact sports.

Figure 2.

BOLD Sequence

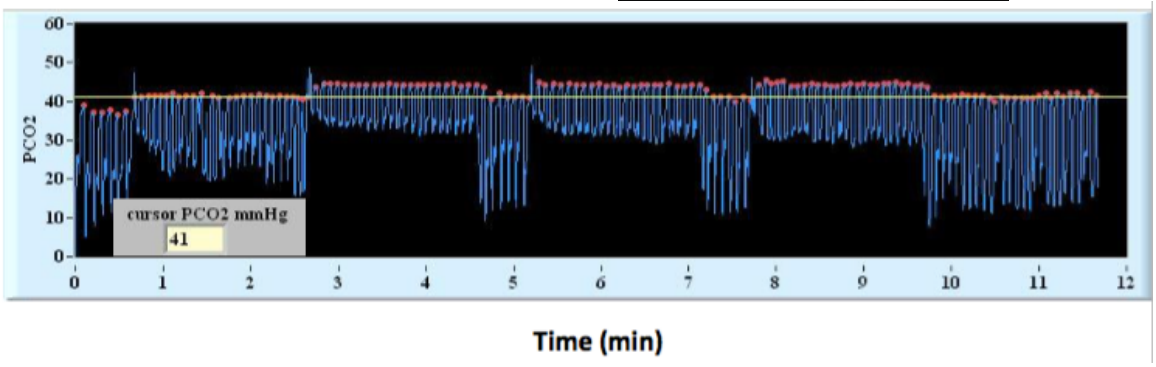


Figure 3.

pCASL sequence

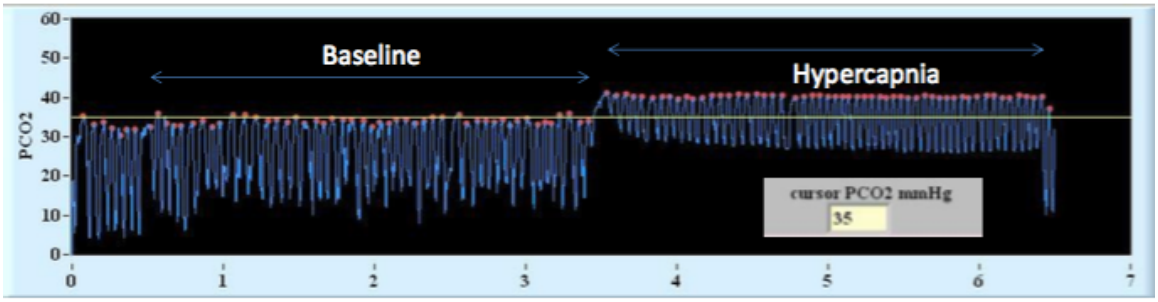


Figure 4.

Group comparisons (A) and individual PCS subjects compared to the control atlas (B) and (C).

Regional differences that are significantly more responsive to the CO2 stimulus are coded in the 'cold' blue hues, while those regions that respond greater than the control atlas are coded in 'warm' orange hues

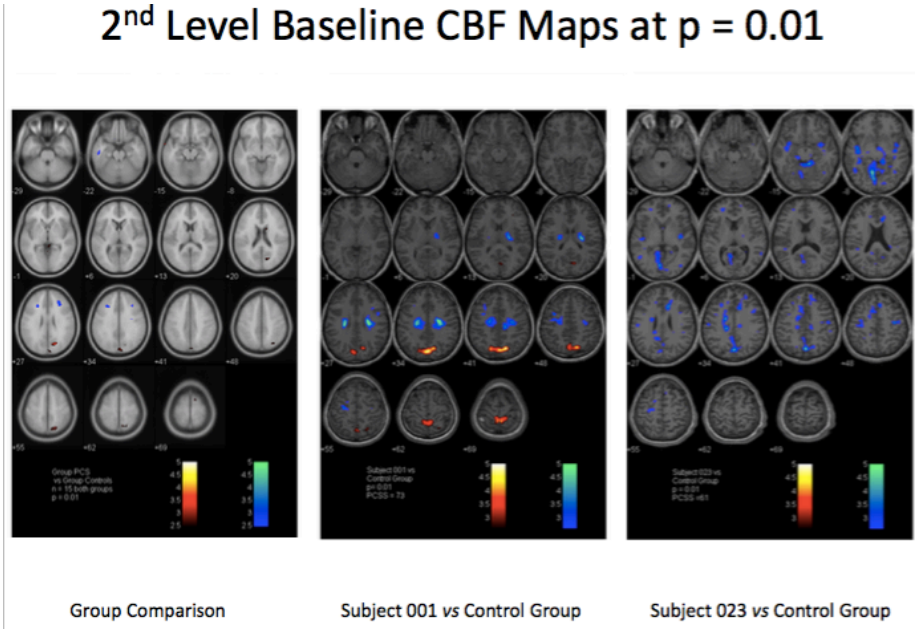


Figure 5.

Group comparisons (A) and individual PCS subjects compared to the control atlas (B) and (C)

Regional differences that are significantly more responsive to the CO2 stimulus are coded in the 'cold' blue hues, while those regions that respond greater than the control atlas are coded in 'warm' orange hues

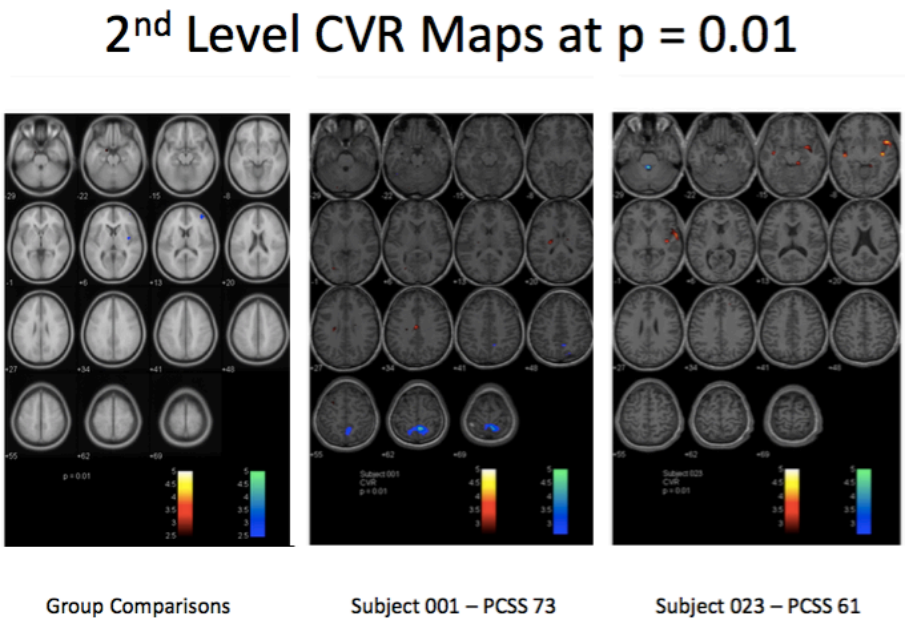


Figure 6.

BOLD 2nd Level Analysis p=0.01
Group voxel comparison of PCS subjects to controls showing a diminished (blue hues) response to the CO2 stimulus.

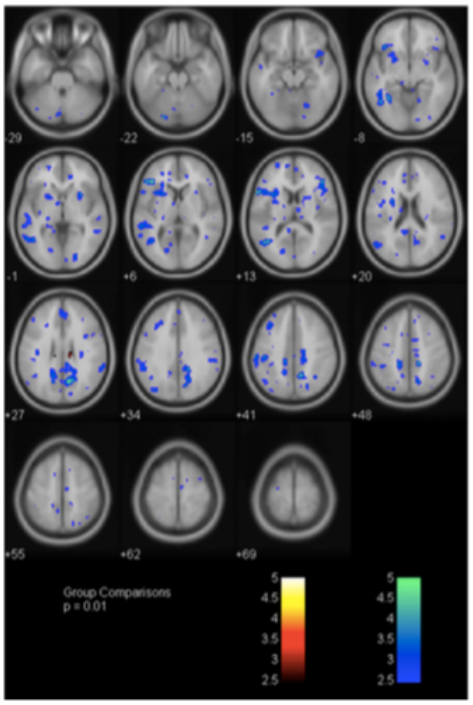


Figure 7.

ROC Curves 2nd Level Analysis p=0.001
ROC Curves for the greater than and less than responses to control atlas

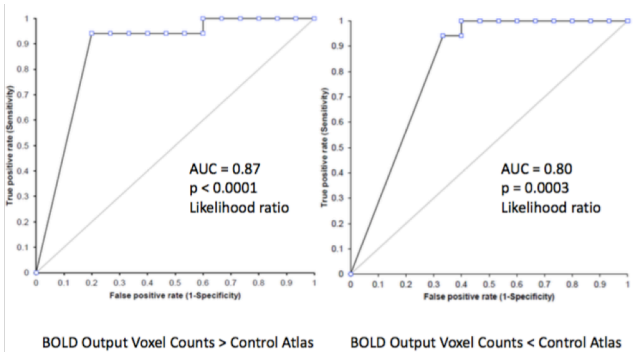


Table 1.

age/sex	sport	symptoms	Clinical indication	Time since injury (days)	MRI details	Results
11M	hockey	headaches	Abnormal CT results	41 days	GRE+, C-, SWI-	Left sylvian fissure arachnoid cyst, right occipital intraparenchymal hemorrhage
17F	soccer	headaches, polydipsia, cold intolerance	Constitutional symptoms	40 days	C+, GRE-, SWI, dynamic pituitary study	Normal
17F	hockey	headache, blurred vision, dizziness	Persistent symptoms	238 days	GRE+, C-, SWI-	Normal
14F	soccer	headache, photophobia, dizziness	Persistent symptoms	183 days	GRE+, C-, SWI-	Normal, cavum septum pellucidum
14M	hockey	blurred vision, headache, vomiting	Focal neurological deficit	9 days	GRE+, C+, SWI-	Multi-focal demyelinating disease, optic neuritis
14F	ringette	headaches	Persistent symptoms	60 days	GRE+, C+, SWI-	Left parietal non-hemorrhagic contusion
14F	hockey	headache, fatigue, sleep disturbance	Persistent symptoms	176 days	GRE-, C-, SWI-	Normal
18F	hockey	headache, dizziness, visual disturbance	Persistent symptoms	170 days	GRE+, TOF MRA	Normal
13F	gymnastics	headache, fatigue, sleep disturbance	Abnormal CT results	14 days	GRE+, C+, MRA	Normal, bilateral basal ganglia calcifications
11M	hockey	headache, dizziness, photophobia	Persistent symptoms	154 days	GRE-, SWI+	Normal
14M	volleyball	Headache, decreased concentration, language processing impairment	Persistent symptoms	180 days	GRE+, C-, SWI-	Normal
15F	basketball	Headache, blurred vision, anxiety	Persistent symptoms	213 days	GRE+, C-, SWI-	Normal
14 M	hockey	migraine headaches	Persistent symptoms	131 days	GRE+, C-, SWI+	Normal
16F	soccer	headaches, blurred vision, dizziness	Persistent symptoms	143 days	GRE+, C-, SWI-	Normal
15F	baseball	headaches	Persistent symptoms	199 days	GRE-, C-, SWI-,	Posterior fossa arachnoid cyst, volume loss left cerebellum, non-specific white matter abnormalities
14F	Figure skating	Headaches, dizziness, anxiety	Persistent symptoms	210 days	GRE+, C-, SWI-	Normal

Table 2:
End-tidal gases and Hemodynamics

	Controls		PCS	
	Mean	SD	Mean	SD
BL_CO_2	38.9	3.2	38.4	2.9
Hyper_CO_2	43.3	3.0	43.0	2.8
Delta CO_2	4.4	0.7	4.6	0.7
BL_O_2	112.0	3.1	114.5	3.3
BL_MAP	74.2	5.7	78.5	9.1
BL_HR	66.1	10.4	71.2	16.4
Hyper_MAP	75.2	6.6	78.6	7.7
Hyper_HR	69.4	11.4	71.6	14.0

Where:
BL = baseline
Hyper = hypercapnia
Delta = mean difference of end-tidal CO_2 between hyper and BL
MAP = mean arterial pressure
HR = heart rate
There were no statistical differences between groups for any variable

Table 3: Voxel counts from 2nd level analysis baseline CBF for greater than or less than at stated p-values

Level	>0.001	<0.001	>0.005	<0.005	>0.01	<0.01	>0.05	<0.05
Voxels PCS	35 (84)	6 (17)	134 (278)	32 (82)	236 (474)	85 (214)	921 (1511)	640 (1230)
Voxels Control	0 (0)	0 (0)	1 (5)	11 (44)	38 (124)	40 (110)	570 (1181)	334 (451)
AUC	0.70	0.57	0.77	0.57	0.70	0.57	0.62	0.52
p-value	0.006	0.207	0.002	0.324	0.031	0.430	0.513	0.451

Table 4: Voxel counts from 2nd level analysis CVR for greater than or less than at stated p-values

Level	>0.001	<0.001	>0.005	<0.005	>0.01	<0.01	>0.05	<0.05
Voxels PCS	50 (107)	59 (186)	137 (276)	175 (466)	209 (406)	269 (645)	698 (1096)	914 (1502)
Voxels Control	0 (0)	0 (0)	2 (7)	0 (0)	18 (24)	3 (7)	579 (548)	195 (197)
AUC	0.70	0.67	0.73	0.80	0.62	0.77	0.46	0.65
p-value	0.006	0.016	0.006	0.0002	0.107	0.003	0.724	0.086