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Quantitative Susceptibility Mapping in Adults with Persistent Postconcussion Symptoms after Mild Traumatic Brain Injury: An Exploratory Study

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ABSTRACT

BACKGROUND AND PURPOSE: It is estimated that 18%–30% of patients with concussion experience symptoms lasting more than 1 month, known as persistent post-concussion symptoms (PPCS). Symptoms can be debilitating, and include headache, dizziness, nausea, problems with memory and concentration, sleep and mood disruption, and exercise intolerance. Previous studies have used quantitative susceptibility mapping (QSM) to show altered tissue susceptibility levels in adults acutely following concussion, however this finding has yet to be investigated in participants with PPCS.

MATERIALS AND METHODS: In this exploratory case-controlled study, we measured tissue susceptibility using QSM in 24 participants with PPCS after mild traumatic brain injury (mTBI) and 23 healthy controls with no history of concussion. We compute tissue susceptibility for 7 white matter tracts and 3 deep gray matter regions and compare tissue susceptibility between groups using ANCOVA models controlling for age and sex. We also assess the relationship between regional tissue susceptibility and symptoms.

RESULTS: There were no significant differences between tissue susceptibility in participants with PPCS compared with control subjects in any of the evaluated regions. However, we show lower tissue susceptibility across 4 white matter tracts was generally associated with worse symptoms in the PPCS group. Specifically, we saw relationships between white matter susceptibility and headache (p = .006), time since injury (p = .03), depressive symptoms (p = .021), and daytime fatigue (p = .01) in participants with PPCS.

CONCLUSIONS: These results provide evidence in support of persistent changes in the brain months to years after injury and highlight the need to further understand the pathophysiology of PPCS, to determine effective prevention and treatment options.

ABBREVIATIONS: ACTBI = Aerobic Exercise for Chronic Symptoms following mild Traumatic Brain Injury; ATR = anterior thalamic radiation; CCB = corpus callosum body; CCG = corpus callosum genu; CCS = corpus callosum splenium; DHI = Dizziness Handicap Inventory; ESS = Epworth Sleepiness Scale; GAD = Generalized Anxiety Disorder; FA = fractional anisotropy; FM = forceps minor; FSS = Fatigue Severity Scale; HIT-6 = Headache Impact Test 6; IFOF = inferior fronto-occipital fasciculus; mTBI = mild traumatic brain injury; RPQ = Rivermead Post Concussion Symptoms Questionnaire; PCSC = Post-Concussion Syndrome Checklist; PHQ = Patient Health Questionnaire; PPCS = persistent post-concussion symptoms; QSM = quantitative susceptibility mapping; SLF = superior longitudinal fasciculus; SE = standard error

Mild traumatic brain injury (mTBI, also known as concussion, the terms will be used interchangeably in this article, consistent with most recent terminology) is the most common form of brain injury, estimated to affect approximately 1.6% of Canadians.[1] Though most people recover within 10–14 days, roughly 18%–31% of adults still have symptoms months to years afterward, known as persistent post-concussion symptoms (PPCS).[2] Symptoms include headache, dizziness, exercise intolerance, nausea, memory deficits, difficulty concentrating, sleep difficulties, and mood disruption.[3] Symptoms can be debilitating, severely impacting quality of life. Treatment options are limited, in part due to poor understanding of PPCS pathophysiology.

mTBI results from a rapid acceleration and deceleration of the brain within the skull. It can cause diffuse axonal injury from shearing of axons, shown by loss of white matter tract integrity on diffusion imaging.[4] mTBI also leads to cascades of neurometabolic events, known as secondary injury processes. This includes stretching of membranes resulting in a flux of ions, followed by

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SUMMARY

PREVIOUS LITERATURE: It is estimated that 18%–31% of adults who experience concussion continue to have symptoms months to years after injury, known as persistent post-concussion symptoms (PPCS). These symptoms can be debilitating and severely affect quality of life; however treatment options are limited due to a lack of understanding of PPCS pathophysiology. Concussion can cause cascades of neurometabolic events, which can result in prolonged pathological processes. Quantitative susceptibility mapping (QSM) can potentially quantify changes in tissue susceptibility related to concussion associated pathological processes. Previous studies using QSM have shown altered tissue susceptibility in acute concussion. Here we investigate QSM measured tissue susceptibility in participants with PPCS.

KEY FINDINGS: Lower tissue susceptibility across 4 white matter tracts was generally associated with worse symptoms in the PPCS group. Specifically, there were significant relationships between white matter susceptibility and headache, time since injury, depressive symptoms, and daytime fatigue in participants with PPCS.

KNOWLEDGE ADVANCEMENT: We interpret this to reflect increased inflammation in participants with PPCS, providing evidence for persistent changes in the brain months to years after injury, and highlighting the need to further understand PPCS pathophysiology, to determine effective prevention and treatment options.

widespread release of several neurotransmitters, particularly excitatory neurotransmitters such as glutamate.[5] This can lead to mitochondrial calcium overload, inducing changes in membrane permeability resulting in production of reactive oxygen species and mitochondrial swelling and dysfunction. As the mitochondria fail, energy production is reduced, resulting in decreased brain metabolism. The excitatory neurotransmitters also activate microglia (gliosis) that release inflammatory cytokines.[3,6] Additionally, mTBI can cause accumulation of iron, particularly in deep gray matter structures, which has been linked with cognitive dysfunction. Iron dysregulation may also lead to further generation of reactive oxygen species, triggering additional inflammatory processes.[6]

It is possible that prolonged pathologic processes associated with secondary injury may be linked to the development of PPCS. However, these secondary injury processes cannot be typically seen using conventional neuroimaging. Quantitative susceptibility mapping (QSM) is an application of MRI that exploits changes in the magnetic properties of tissue to measure differences in tissue susceptibility. QSM can therefore potentially quantify changes in tissue susceptibility related to mTBI-associated pathological processes, such as demyelination, accumulation of iron and calcium, and gliosis.[7] Using QSM, previous studies have shown that, compared with controls, participants 8 days post-concussion have altered global white matter susceptibility,[8,9] as well as altered tissue susceptibility in multiple white matter tracts.[8] Additionally, tissue susceptibility in frontal white matter 10 days post-injury was shown to predict persistent symptoms 4 weeks post-injury.[10]

QSM-measured tissue susceptibility may provide new insight into the role of sustained pathological processes in PPCS. To our knowledge, there have been no studies using QSM to investigate tissue susceptibility in PPCS. This exploratory study compared tissue susceptibility from select gray matter regions and white matter tracts between participants with PPCS following mTBI and healthy controls, as well as assessing the relationship between tissue susceptibility and symptom severity. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist guided reporting of this article and has been included in the Online Supplemental Data.

MATERIALS AND METHODS

Study Design

This cross-sectional case-controlled study was nested within the Aerobic Exercise for Chronic Symptoms following Mild Traumatic Brain Injury (ACTBI) trial, registered at clinicaltrials.gov (NCT03895450). The study protocol was approved by the Conjoint Health Research Ethics Board at the University of Calgary (REB18-1329). All participants provided written, informed consent. ACTBI trial methods are detailed in Mercier et al,[13] with the relevant details described below.

Participant Population

Participants with PPCS were recruited from the Calgary Brain Injury Program and Calgary Pain Center between May 2019 and December 2023. Recruitment was paused between March 2020 and June 2021 due to the COVID-19 pandemic. Eligibility criteria for the PPCS cohort included: 1) aged 18–65 years, 2) diagnosis of mTBI based on the American Congress of Rehabilitative Medicine criteria,[11] 3) diagnosis of PPCS based on the International Classification of Diseases-10 post-concussional syndrome criteria,[12] 4) at least 3 months to no more than 5 years since most recent mTBI, 5) exercise intolerance defined as acute exacerbation of post-concussive symptoms with exercise, evaluated by using the Buffalo Concussion Treadmill Test,[13,14] and 6) maintenance of a stable pharmacologic regimen for at least 1 month before study participation. Participants with PPCS had no sustained loss of consciousness greater than 30 minutes post-injury, a Glasgow Coma Scale score less than 13, and post-traumatic amnesia for less than 24 hours post-injury, as per the American Congress of Rehabilitative Medicine criteria for mTBI.[11] Participants with PPCS were excluded if they had a history of moderate to severe traumatic brain injury, cardiopulmonary, or musculoskeletal condition.

Age (±3 years) and sex-matched controls without any history of concussion were recruited from the community using posters and word of mouth advertising. All control participants were

screened to rule out any neurologic conditions, including history of suspected concussion/traumatic brain injury or major psychiatric history. All participants were screened to rule out contraindications to MRI.

As stated above, this study was part of a larger trial. Participants with PPCS were age and sex matched to healthy control participants at recruitment. Participants were only included in the present study if they completed a T1-weighted structural scan and a QSM scan during the MRI portion of the trial. QSM data were collected in 33 participants with PPCS and 30 age- and sex-matched controls with no lifetime history of brain injury.

Questionnaires

Demographic and injury characteristic data were collected in the form of self-reports. Participants with PPCS completed the following questionnaires: Rivermead Post Concussion Symptoms Questionnaire (RPQ, mTBI symptom burden), Post-Concussion Syndrome Checklist (PCSC, mTBI symptom frequency, intensity, and duration), Headache Impact Test-6 (HIT-6, functional impact of headache), and the Dizziness Handicap Inventory (DHI, dizziness handicap).

Additionally, all participants (participants with PPCS and control participants) completed the following clinical questionnaires: Patient Health Questionnaire-9 (PHQ-9, depressive symptoms), Generalized Anxiety Disorder-7 Scale (GAD-7, anxiety symptoms), Fatigue Severity Scale (FSS, fatigue), and Epworth Sleepiness Scale (ESS, daytime sleepiness). Detailed description and citations for all questionnaires can be found in Mercier et al.[13]

Data Acquisition

QSM data were obtained on a 3 T MR scanner (GE Healthcare 750w) by using a 32-channel head coil. A T1-weighted structural image was acquired using a BRAVO sequence (TR/TE/TI = 7.30/2.70/600 ms, matrix size = 256 × 256, FOV = 252 × 278 mm^2, slice thickness = 1 mm, flip angle = 10°). QSM data were acquired with a multiecho gradient-echo sequence using the following parameters: TR = 56.7 ms, 10 echoes with echo spacing 5.3 ms with TE ranging from 4.5–52.2 ms, matrix size = 256 × 256, FOV = 240 × 240 mm^2, 1.9 mm slice thickness, unipolar readout gradient, and acceleration factor of 2.5. Complex-value QSM images were reconstructed and saved.

Data Processing

QSM data were processed using a customized, well-validated, and robust QSM processing pipeline[15] that has been used extensively.[10,16–18] Processing included brain extraction on the magnitude and phase images using FSL BET (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BET),[19] phase unwrapping using BESTPATH,[20] weighted least squares calculation of the field from the phase, background field removal with RESHARP,[21] and dipole inversion with Total Variation (TV) TV regularization.[22] QSM data were registered to Montreal Neurological Institute space using FSL FLIRT (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FLIRT).[23]

White matter masks were generated using the Harvard-Oxford[24] and Johns Hopkins[25] atlases for the following regions: global white matter, anterior thalamic radiation (ATR), cingulum (CH), forceps minor (FM), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), corpus callosum (separated into the corpus callosum body [CCB], corpus callosum genus [CCG], and corpus callosum splenium [CCS]); several of these regions have shown altered susceptibility after concussion.[8] We also evaluated the 3 subcortical gray matter regions: caudate, putamen, and pallidum. Masks for these regions were generated using the Harvard-Oxford Subcortical Atlas.[24] Mean tissue susceptibility values were computed from each region for each subject. See Online Supplemental Data for masks.

Statistical Analysis

Statistical analyses were conducted using R (Version 4.1.2, R Core Team 2020 https://www.R-project.org/). Age was compared between groups using a t test and sex was compared using a χ^2 test. ANCOVA tests were used to compare tissue susceptibility for each region between groups (PPCS versus control) while controlling for age and sex. Partial correlations were used to assess the relationship between tissue susceptibility in each region and PPCS burden, while also controlling for age and sex (in participants with PPCS only). Linear models were used to assess the relationship between tissue susceptibility and clinical questionnaire scores in the full sample, including a group by symptom score interaction. Age and sex were included as fixed factors (notation for full model using the lm function in R: QSM∼questionnaire*group + age + sex). Due to the lack of previous research in this area and the exploratory nature of this study, we did not correct for multiple comparisons.[26]

RESULTS

Sample Characteristics

Nine participants from the PPCS group and 7 participants from the control group were excluded due to poor quality QSM data, for example presence of streaking artifacts.

See Table 1 for demographic information of the entire sample and Table 2 for injury characteristics of the PPCS group.

Group Comparisons

There were no significant differences between groups (PPCS versus control) in tissue susceptibility values from any of the evaluated regions (Fig 1).

QSM and PPCS Burden

There were no significant relationships between tissue susceptibility in the subcortical gray matter regions and PPCS burden. Participants with PPCS with higher functional burden of headache were found to have lower susceptibility in the CCB (R_p = −0.57, p = .006) (Fig 2*A*). Participants with PPCS with a longer time since injury had lower tissue susceptibility measures in the SLF (R_p = −0.47, p = .03) (Fig 2*B*). There were no other significant relationships between white matter tract susceptibility and PPCS burden.

QSM and Clinical Questionnaires

Depressive Symptoms. There was a significant group by depressive symptom score interaction on susceptibility in the CCS (b = 0.001, standard error [SE] = 0.0005, p = .02; Online Supplemental Data). Depressive symptoms were related to susceptibility in participants with PPCS only, with no significant relationship seen

Table 1: Demographic characteristics of participants in the PPCS and control groups

Demographics	PPCS Group (n = 24)	Control Group (n = 23)	p Value
Age, mean (SD)	43.00 (12.12)	41.76 (11.10)	.72
Sex, M/F	5/19	4/17	.88
Education, n (%)			
PhD/medical doctorate	2 (8%)	1 (4%)	
Masters degree	6 (25%)	2 (9%)	
Bachelors degree	11 (46%)	9 (39%)	
Trade school/vocational education	3 (13%)	8 (34%)	
Grade 12	2 (8%)	1 (4%)	
Other	0 (0%)	2 (9%)	.21
Current work status, n (%)			
Full-time (employed or student)	11 (46%)	18 (78%)	
Part-time (employed or student)	4 (17%)	3 (13%)	
Not currently working (employed or student before accident)	7 (29%)	0 (0%)	
Not employed or student	1 (4%)	1 (4%)	.03
Questionnaires, mean (SD)			
Depressive symptoms, PHQ-9 [scoring range: 0–27]	11.58 (5.83)	3.81 (4.13)	<.001
Anxiety symptoms, GAD-7 [scoring range: 0–21]	6.42 (4.73)	2.86 (2.99)	.006
Fatigue, FSS [scoring range: 9–63]	43.08 (14.93)	23.81 (11.10)	<.001
Daytime sleepiness, ESS [scoring range: 0–24]	9.79 (4.54)	3.95 (2.60)	<.001

Note:—ESS indicates Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; GAD-7, Generalized Anxiety Disorder 7; PHQ-9, Patient Health Questionnaire-9; SD, standard deviation.

Table 2: Summary of patient injury characteristics and symptom scores

Injury Characteristics and Symptom Questionnaires	
Months since injury, mean (range)	27.13 (4–58)
Mechanism of injury, n (%)	
Sports/recreational play	5 (21%)
Motor vehicle collision	11 (46%)
Fall	6 (25%)
Assault	0 (0%)
Work related	1 (4%)
Other	1 (4%)
Loss of consciousness, n (%)	
Yes	8 (33%)
No	13 (54%)
Unknown	3 (13%)
Number of lifetime mTBIs, mode (range)	1 (1–5+)
Medications, n (%)	
Antidepressant/antipsychotic/neurostimulant	15 (63%)
Antiepileptic	3 (13%)
Antinausea/gastrointestinal	6 (25%)
Cardiovascular	1 (4%)
Endocrine	2 (8%)
Headache	8 (33%)
Hormone replacement therapy	1 (4%)
Metabolic	2 (8%)
Pain	6 (25%)
Respiratory/antihistamine	3 (13%)
Sleep	7 (29%)
Questionnaires, mean (SD)	
RPQ [scoring range: 0–64]	33.00 (10.08)
PCSC [scoring range: 30–150]	91.92 (19.46)
HIT-6 [scoring range: 36–78]	62.29 (6.23)
DHI [scoring range: 0–100]	31.17 (23.39)

Note:—DHI indicates Dizziness Handicap Inventory; HIT-6, Headache Impact Test; PCSC, Post-concussional Syndrome Checklist; RPQ, Rivermead Post Concussion Symptoms Questionnaire; SD, standard deviation.

in the control group (Fig 3*A*). Depressive symptoms were significantly associated with susceptibility levels in the FM in the full sample ($b = -0.0009$, SE = 0.0004, $p = .02$; Online Supplemental Data), with no significant group by depressive symptom interaction ($b = -0.0007$, SE = 0.0004, $p = .09$; Fig 3*B*).

Anxiety Symptoms. Anxiety symptoms were significantly associated with susceptibility levels in the ATR in the full sample ($b = -0.0007$, SE = 0.0003, $p = .04$; Online Supplemental Data), with no significant group by anxiety score interaction ($b = 0.0004$, SE = 0.0004, $p = .3$; Fig 4*A*). There was a significant group by anxiety symptom score interaction on susceptibility in the FM ($b = -0.001$, SE = 0.0005, $p = .05$; Online Supplemental Data). Anxiety symptoms were related to susceptibility in the FM in the control group only, with no significant relationship seen in participants with PPCS (Fig 4*B*).

Daytime Fatigue. Daytime fatigue symptoms were significantly associated with susceptibility levels in the CCG in the full sample ($b = 0.0002$, SE = 0.0001, $p = .04$; Online Supplemental Data). There was no significant group by fatigue symptom score interaction ($b = -0.0002$, SE = 0.0001, $p = .08$; Fig 5*A*). There was a significant group by fatigue symptom score interaction on susceptibility in the CCS ($b = -0.0005$, SE = 0.0002, $p = .01$; Online Supplemental Data). Fatigue symptoms were related to susceptibility in participants with PPCS only, with no significant relationship seen in the control group (Fig 5*B*). There was also a significant group by fatigue symptom score interaction on susceptibility in the IFOF ($b = -0.0001$, SE = 0.00007, $p = .04$; Online Supplemental Data). Fatigue symptoms were related to susceptibility in the control group only, with no significant relationship seen in participants with PPCS (Fig 5*C*).

Daytime Sleepiness. There were no significant relationships between daytime sleepiness and susceptibility in any evaluated region.

DISCUSSION

This exploratory study quantified tissue susceptibility in selected subcortical gray matter regions and white matter tracts in participants with PPCS following mTBI and a healthy control group (without history of diagnosed/suspected brain injury). We show susceptibility in the CCB and SLF tracts of participants with PPCS was associated with functional impact of headache and time since injury, respectively. Susceptibility in white matter tracts was also associated with clinical characteristics across both groups, specifically depression, anxiety, and fatigue.

Tissue susceptibility describes the response of an object when placed in a magnetic field. QSM generates images based on

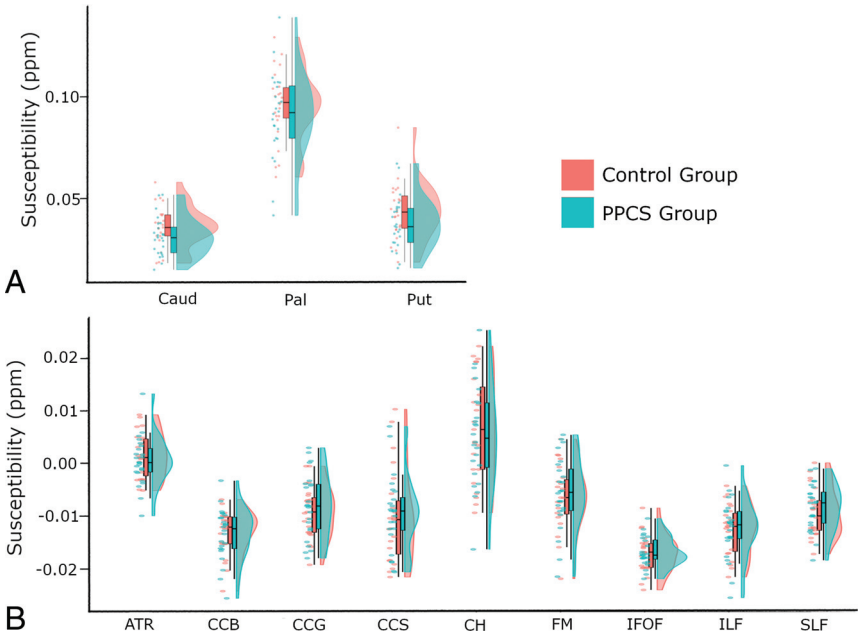

FIG 1. *A*, Comparison between groups (PPCS versus control) of susceptibility values from individual gray matter regions. *B*, Comparison between groups of susceptibility values from individual white matter tracts. There were no significant differences between groups in any gray matter region or white matter tract. Caud = caudate; Pal = pallidum; Put = putamen.

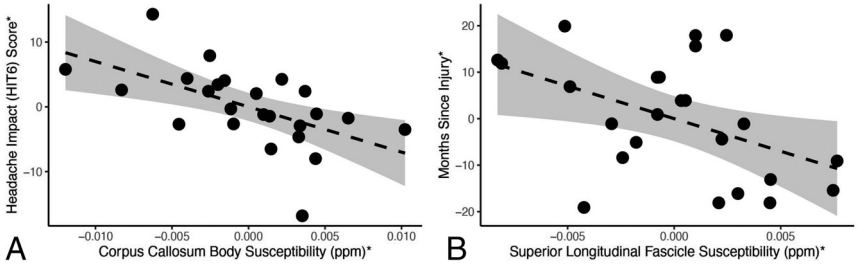

FIG 2. *A*, Significant relationship between susceptibility in the CCB and the headache impact score, measured by using the HIT-6 ($R_p = -0.57$, $p = .006$). *B*, Significant relationships between susceptibility in the SLF and months since injury ($R_p = -0.47$, $p = .03$). *For visualization of partial correlations, the residuals from a regression against age and sex are plotted, to remove variability from these factors.

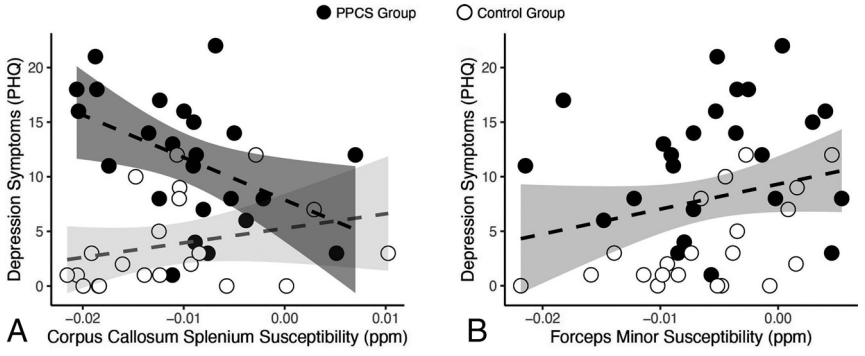

FIG 3. *A*, Relationship between depressive symptoms and susceptibility in the CCS in both the patient and control groups. There was a significant group by depressive symptom interaction on susceptibility in the CCS ($b = 0.001$, SE = 0.0005, $p = .02$). Depressive symptoms were related to CCS susceptibility in participants with PPCS only. *B*, Significant relationship between depressive symptoms and susceptibility in the FM in the full sample (PPCS plus control group) ($b = -0.0009$, SE = 0.0004, $P = .02$). PHQ = Patient Health Questionnaire.

magnetic field variations in the tissue when placed in the MRI scanner. For example, positive tissue susceptibility can be a marker of iron deposition, hemorrhage, edema, or loosening of the myelin sheath, and negative tissue susceptibility can be a marker of calcium accumulation/calcification, or an increase in myelin.[6]

We found relationships between tissue susceptibility in the PPCS group and symptom burden, with lower tissue susceptibility across multiple white matter tracts generally associated with worse symptoms. The directionality of this finding is in line with animal models of brain injury. Chary et al[7] showed a decrease in tissue susceptibility in the corpus callosum in rodent models 6 months after injury. In the same area they found increased cell density, attributed to gliosis, and an increase in the density of myelinated axons.[7] Gliosis can help regulate the inflammatory response but can also release free radicals and proinflammatory cytokines. A sustained inflammatory state is a significant contributor to secondary damage and neurologic impairments.[27] Participants with PPCS with more severe symptoms may therefore be experiencing higher levels of sustained inflammation. Indeed, previous literature shows participants with PPCS have higher levels of inflammatory markers in CSF[28] and blood samples.[29]

Higher functional impact of headache was associated with lower CCB susceptibility. The corpus callosum is the largest white matter structure in the brain and serves as the primary interhemispheric bridge.[30] Computer simulations of concussion show that the greatest shear and strain forces occur in this region,[31] and damage to this area is one of the most commonly reported pathologic changes after brain injury.[4] Previous research shows decreased fractional anisotropy (FA) of the corpus callosum after concussion is correlated with prolonged symptomology, in line with our findings. Participants with lower FA in the CCG and CCB recovered significantly more slowly from cognitive symptoms, and participants with lower FA in the CCS recovered more slowly from depressive

symptoms.[30] Participants with increased FA in the CCG and decreased FA in the CCS were also more likely to have post-traumatic headache after concussion.[32]

A longer time since injury was associated with lower SLF susceptibility. The SLF is the largest associative fiber bundle system in the brain,[33] with many tracts that connect most parietal regions to the frontal lobe.[34] Along with the corpus callosum, the SLF is another tract frequently reported to distinguish participants with PPCS from controls.[4] The relationship between SLF tissue susceptibility and time since injury may reflect sustained inflammation that continuously increases as the brain attempts to heal.

Participants with PPCS with lower CCS susceptibility had higher depressive symptoms. Changes in CCS microstructure have been shown to be related to persistent depression after concussion.[30] The CCS connects parietal, inferior, and medial temporal cortices.[35] This includes the posterior cingulate cortex, an area involved in emotional processing, and a key region of the default mode network. Alterations here can result in an inability to regulate the balance of internal versus external attention, and has been linked with excessive rumination in depression.[36]

Across the full sample, higher FM susceptibility was associated with higher depressive symptoms. FM integrity has been previously linked with depression in patients with MS.[37] The FM connects the dorsolateral prefrontal cortices, which have been frequently linked to depression.[37] Additionally, higher FM susceptibility was associated with higher anxiety symptoms in the control group only. Higher anxiety symptoms were also associated with lower ATR susceptibility. Both regions have been linked to anxiety in healthy individuals. For example, Lu et al[38] found healthy adults who had higher trait anxiety scores had lower white matter integrity in these regions. The ATR connects the prefrontal lobe to the thalamus, and thalamocortical connectivity plays a key role in many aspects of anxiety such as threat bias, hyperarousal, and avoidance.[39]

In the control group, higher IFOF susceptibility was associated with higher daytime fatigue symptoms. T1-weighted intensity of the IFOF has previously been associated with sleep quality in patients with chronic fatigue syndrome,[40] suggesting it has a role in sleep/fatigue. Higher fatigue scores were also associated with higher CCG susceptibility in the full sample, and lower CCS susceptibility in the PPCS group. Atrophy of the corpus callosum[41] and a higher lesion load in this area[42] has been associated with fatigue in MS. The authors postulate that impaired communication between brain regions resulting from white matter atrophy results in an increased cortical load to compensate, contributing to fatigue.[42]

In contrast to the previous 2 papers by Koch et al[8,9] measuring tissue susceptibility in acute concussion, we found no

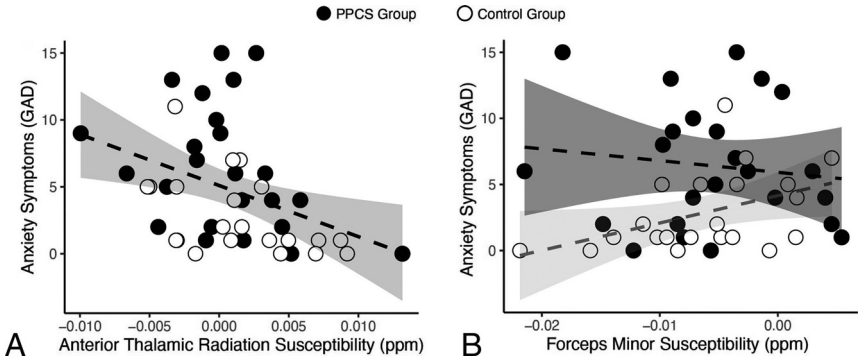

FIG 4. *A*, Significant relationship between anxiety symptoms and susceptibility in the ATR in the full sample (PPCS plus control group) ($b = -0.0007$, SE = 0.0003, $p = .04$). *B*, Relationship between anxiety symptoms and susceptibility in the FM in both the patient and control groups. There was a significant group by anxiety symptom score interaction ($b = -0.001$, SE = 0.0005, $p = .05$) on susceptibility in the FM. Anxiety symptoms were related to FM susceptibility in the control group only. GAD = Generalized Anxiety Disorder.

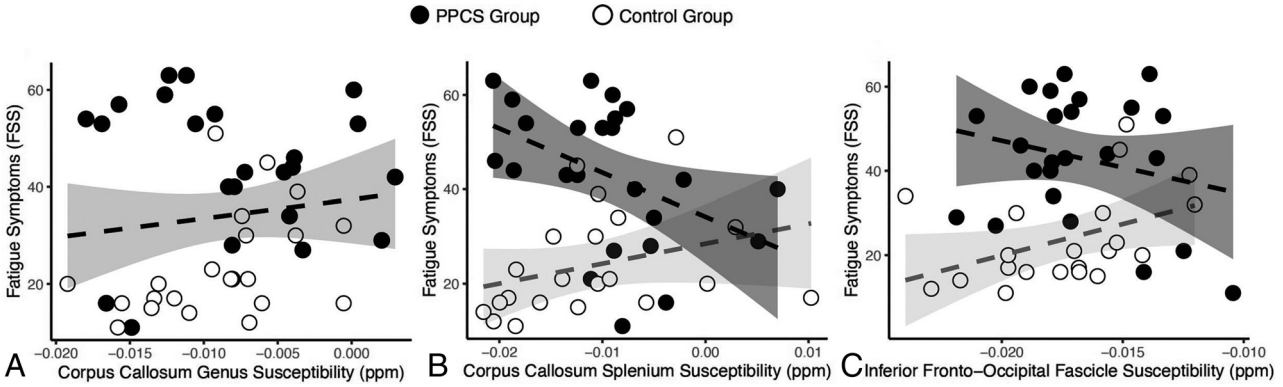

FIG 5. *A*, Significant relationship between daytime fatigue symptoms and susceptibility in the CCG in the full sample (PPCS plus control group) ($b = 0.0002$, SE = 0.0001, $p = .04$). *B*, Relationship between fatigue symptoms and susceptibility in the CCS in both the patient and control groups. There was a significant group by fatigue symptom score interaction ($b = -0.0005$, SE = 0.0002, $p = .01$) on susceptibility in the CCS. Fatigue symptoms were related to CCS susceptibility in participants with PPCS only. *C*, Relationship between fatigue symptoms and susceptibility in the IFOF in both the patient and controls groups. There was a significant group by fatigue symptom score interaction ($b = -0.0001$, SE = 0.00007, $p = .04$) on susceptibility in the IFOF. Fatigue symptoms were related to IFOF susceptibility in the control group only. FSS = Fatigue Severity Scale.

group differences in susceptibility between patients with PPCS and controls. Koch et al[8] imaged participants 24 hours, 8 days, and 6 months after injury, and Koch et al[9] imaged participants 48 hours after injury. The sample in our study was imaged on average 2 years after injury, therefore, it is possible that any changes have resolved at this point. A second potential reason is due to differences in recruited populations. The average age of participants in the previous studies was 18 years, substantially younger than our population, which had a mean age of 43 years. Furthermore, Koch et al[8] compared 28 controls to 28 injured athletes, and Koch et al[9] compared 78 controls to 78 injured athletes. Though not much smaller than the Koch et al[8] group (24 patients with PPCS versus 23 controls), it is possible that effect sizes of group differences may decrease over time, and our study may be underpowered to detect them. Given $\alpha = 0.05\%$ and 80% power, this study is powered to detect an effect size of 0.42. This is similar to the effect sizes seen at earlier time points in Koch et al in 2018,[8] however future studies should aim to include a larger sample size to ensure adequate power. Larger sample sizes will also be able to probe more specific relationships, such as the impact of medication. Furthermore, most of our sample obtained their injury from a motor vehicle collision, which may result in different injury processes than sport-related concussion.

Additionally, interpreting tissue susceptibility differences is challenging because these measures are influenced by multiple processes in the brain. Therefore, both higher and lower tissue susceptibility can reflect pathological processes (such as calcification, inflammation, iron deposition) as well as normal brain structures (such as myelin density). Future studies can include other imaging measures to complement QSM findings, such as diffusion imaging or T2 mapping, to aid in interpretation.

A limitation of this study is that we did not correct for multiple comparisons; this was due to the exploratory nature of our study. Because this is the first study to investigate the relationship between PPCS following mTBI and QSM-measured tissue susceptibility, we included multiple white matter tracts and gray matter regions in our comparisons, as well as multiple questionnaires, resulting in many comparisons. Due to the small number of subjects in our sample, this study is not powered to control for the large number of comparisons conducted. Subsequently, some of these results may be spurious effects, and replication is needed to strengthen confidence in these findings. Future studies can use our findings to guide their studies to probe for specific relationships. Additionally, the use of multiple questionnaires in this study can be used to inform design of future mechanistic studies examining PPCS symptom pathophysiology.

CONCLUSIONS

We provide evidence for alterations in white matter tissue susceptibility in participants with PPCS following mTBI compared with healthy controls. We show that tissue susceptibility levels in white matter tracts are correlated with specific postconcussive symptoms, providing evidence for persistent changes in the brain months to years after injury, and highlighting the need to further understand PPCS pathophysiology to determine effective prevention and treatment options.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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