

Decreased Number of Self-Paced Saccades in Post-Concussion Syndrome Associated with Higher Symptom Burden and Reduced White Matter Integrity

Foad Taghdiri,^{1,2} Jonathan Chung,³ Samantha Irwin,⁴ Namita Multani,¹ Apameh Tarazi,^{5,6}
Ahmed Ebraheem,⁶ Mozghan Khodadadi,⁶ Ruma Goswami,^{6,7} Richard Wennberg,^{5,6}
David Mikulis,^{2,6,8} Robin Green,^{2,6,9} Karen Davis,^{2,6,7,11} Charles Tator,^{2,6,7,10}
Moshe Eizenman,^{3,12,13} and Maria Carmela Tartaglia^{1,2,5–7}

Abstract

The aim of this study was to examine the potential utility of a self-paced saccadic eye movement as a marker of post-concussion syndrome (PCS) and monitoring the recovery from PCS. Fifty-nine persistently symptomatic participants with at least two concussions performed the self-paced saccade (SPS) task. We evaluated the relationships between the number of SPSs and 1) number of self-reported concussion symptoms, and 2) integrity of major white matter (WM) tracts (as measured by fractional anisotropy [FA] and mean diffusivity) that are directly or indirectly involved in saccadic eye movements and often affected by concussion. These tracts included the uncinate fasciculus (UF), cingulum (Cg) and its three subcomponents (subgenual, retrosplenial, and parahippocampal), superior longitudinal fasciculus, and corpus callosum. Mediation analyses were carried out to examine whether specific WM tracts (left UF and left subgenual Cg) mediated the relationship between the number of SPSs and 1) interval from last concussion or 2) total number of self-reported symptoms. The number of SPSs was negatively correlated with the total number of self-reported symptoms ($r = -0.419$, $p = 0.026$). The number of SPSs were positively correlated with FA of left UF and left Cg ($r = 0.421$, $p = 0.013$ and $r = 0.452$, $p = 0.008$; respectively). FA of the subgenual subcomponent of the left Cg partially mediated the relationship between the total number of symptoms and the number of SPSs, while FA of the left UF mediated the relationship between interval from last concussion and the number of SPSs. In conclusion, SPS testing as a fast and objective assessment may reflect symptom burden in patients with PCS. In addition, since the number of SPSs is associated with the integrity of some WM tracts, it may be useful as a diagnostic biomarker in patients with PCS.

Keywords: concussion; oculomotor function; post-concussion syndrome; saccades; white matter

Introduction

CONCUSSION OR MILD TRAUMATIC BRAIN INJURY is often associated with physical symptoms (e.g., headache, dizziness), and emotional (e.g., mood, anxiety) and cognitive impairments (e.g., memory, attention).¹ Most concussed individuals recover within 7–10 days after the injury. However, 10–15% of patients suffer symptoms for months, years, or even indefinitely.² Persistence of concussion-related symptoms beyond the expected recovery period is referred to as post-concussion syndrome (PCS). Despite the debilitating impact of PCS on patients' lives, a reliable

objective biomarker to aid diagnosis and monitor recovery over time is still lacking.

Changes in white matter (WM) integrity, as measured by diffusion tensor imaging (DTI), have been demonstrated in concussed patients in both the acute and chronic phases of injury,^{3–5} but inconsistent results to date on the relationship between DTI WM integrity and concussion-related symptoms have precluded use of DTI as a biomarker.^{6,7} In addition to neuroimaging, neuropsychological testing also is used for evaluating PCS patients.^{8–10} However, many studies have shown limited sensitivity and specificity of neuropsychological testing to the subtle cognitive changes of PCS.^{7,11–13}

¹Tanz Centre for Research in Neurodegenerative Diseases, ²Institute of Medical Science, ³Department of Electrical and Computer Engineering, ⁴Department of Rehabilitation Sciences, ⁵Department of Surgery, ⁶Department of Ophthalmology, ⁷Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada.

⁸Department of Neurology, Hospital for Sick Children, Toronto, Ontario, Canada.

⁹Division of Neurology, ¹⁰Canadian Concussion Centre, ¹¹Division of Neurosurgery, Toronto Western Hospital, Krembil Neuroscience Centre, ¹²Krembil Research Institute, ¹³Division of Neuroradiology, Joint Department of Medical Imaging, University Health Network, Toronto, Ontario, Canada.

Visual complaints such as double vision and eye fatigue, as well as impairment in vergence, accommodation, and saccades, are commonly seen in patients after concussion.^{14–17} Several studies have reported impaired saccadic eye movements in patients with PCS when compared with healthy individuals.^{7,18,19} The self-paced saccade (SPS) task is commonly classified as a type of volitional saccade assessment in which one is asked to execute as many saccades as possible between two stationary visual targets in a fixed amount of time.²⁰ Controlling of SPSs employs different cortical and subcortical areas of the brain. The frontal eye fields (FEF) are essential for triggering volitional saccades by disengaging fixation in SPS task.^{21,22} The supplementary eye fields (SEF) and dorso-lateral prefrontal cortex (DLPFC) also have been shown to be involved in volitional saccades.^{22–25} Finally, the anterior cingulate cortex (ACC) seems to play a crucial role in controlling volitional saccades by maintaining the patient's motivation to complete the SPS task.²⁶

The superior longitudinal fasciculus (SLF), cingulum tract (Cg), and corpus callosum (CC), in particular its anterior segments, are WM tracts important for communication between the FEF, SEF, DLPFC, and ACC and other cortical areas. The CC is the largest WM tract in the brain and is responsible for interhemispheric communication and is often implicated in DTI studies of concussion and PCS.^{27–31} The SLF connects the frontal lobe/DLPFC with parietal regions implicated in the attentional network³² and the Cg connects the cingulate gyrus and DLPFC with structures in the temporal lobe, including parahippocampal cortices and amygdala.^{33,34} The uncinate fasciculus (UF) is another major WM tract that projects bidirectionally from orbitofrontal cortex to anterior temporal lobe.^{4,35} This tract has been reported to play a crucial role in learning associated with repeated exposure to a particular visual task.^{36,37} In addition, integrity of the UF has been shown to be affected in patients with multiple concussions and is related to their impulsive behavior.⁴ Given that, these four WM tracts seem to be the major ones that are involved in volitional controlling of the SPSs.

We hypothesized that cerebral changes that are causing PCS following brain injury can be detected with oculomotor function testing. The aim of this study was to test this hypothesis by assessing the relationship between SPS eye movements, symptoms burden, and the integrity of WM tracts in patients with PCS to examine the potential utility of the SPS metrics as a marker of PCS and monitoring the recovery from PCS.

Methods

Participants

Participants with a history of two or more concussions were recruited from a concussion clinic at the University Health Network (UHN), Toronto, Ontario. Fifty-nine participants with persisting post-concussive symptoms of more than 3 months were included in the study. Two recruited participants had their last concussion 1 month prior to the testing; however, both had been diagnosed with PCS prior to the last concussion.

Verification of original concussions were based on participants' self-report of a blow to the head or the body or the exertion of acceleration/deceleration forces to the head that results in any of the following symptoms: headache, nausea/vomiting, dizziness/balance problems, drowsiness, trouble sleeping, fatigue, sensitivity to noise or light, blurred vision, memory difficulty, and trouble concentrating.^{38,39} Diagnosis of PCS was made by M.C.T (a neurologist at UHN) or C.T (a neurosurgeon at UHN) based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV) criteria for post-concussional

disorder.⁴⁰ Key exclusion criteria were the inability to recall the cause of their concussions, history of neurological or psychiatric disorder or other illness affecting the brain, developmental disorders, or any lesions on routine magnetic resonance imaging (MRI) or computed tomography scans. All participants included in this study completed a neurological examination, neuropsychological assessment, neuroimaging, and oculomotor function testing. The Research Ethics Board of the UHN approved the study. Consent was obtained from all participants, as outlined by the UHN research protocol.

Self-reported outcomes

During the assessment, participants were asked to report on the presence or absence of persistent concussive symptoms and the extent to which these symptoms affected their everyday functioning, if present. The symptoms the participants were questioned on fell into the following domains which comprise the most commonly encountered physical, emotional, and/or cognitive symptoms in PCS^{1,41}: memory, executive function, language, visuospatial, behavior, motor (e.g. weakness, balance), sensory (e.g., numbness), constitutional (e.g., fatigue, dizziness, sensitivity to noise and/or light), and neck pain/headache (Supplementary Table 1; see online supplementary material at <http://www.liebertpub.com>). These domains were selected to be consistent with DSM-IV criteria to define PCS⁴⁰ (impaired attention or memory, fatigue, dizziness, irritability, aggression, anxiety, personality changes, or apathy), as well as the sport concussion assessment tool (SCAT),^{42,43} which is widely being used in the field of concussion research.^{44,45} In addition, since repeated concussion is a risk factor for neurodegeneration^{46,47} and some participants are years out from their last concussion, domains affected in various neurodegenerative diseases such as language, visuospatial, and motor were included. Each domain consisted of several statements and the participants were asked to respond to items using a 3-point scale: “0 – no problem,” “1 – symptom exists but does not interfere with day-to-day life,” or “2 – symptom exists and interferes with day-to-day function.” The total number of symptoms in each domain was calculated by summing all the symptoms reported in the individual domains (symptoms rated either 1 or 2). It should be noted that since the number of symptoms varies across the nine domains, we did not compare differences among domains but only investigated the relationship between domain total and the number of SPSs. Finally, total number of symptoms was calculated by adding the number of symptoms in the domains together.

Neuropsychological testing

All participants underwent a comprehensive neuropsychological battery administered by a trained psychometrist. For the purpose of this study, the following measures were included to provide characterization of visual attention and scanning functions: Trail Making Test Part A (TMT-A), Trail Making Test Part B (TMT-B),^{48,49} Visuospatial Span-backward (VS-backward), and Digit Span-Backward (DS-backward).^{50,51} These measures of executive function were selected because PCS is associated with executive deficits.^{39,52}

Oculomotor function testing

Oculomotor data were collected using Visual Attention Scanning Technology (VAST, EL-MAR Inc.).^{53,54} This eye tracking system consisted of three infrared (IR) light sources, an IR video camera, and a processor. The system was affixed to a 23" monitor. Participants were seated 65 cm from the monitor while head was not fixed, and their binocular gaze positions were estimated 30 times/sec with an accuracy of 0.5° in visual angle.⁵⁵ Following a calibration procedure, the participants were instructed to look at a

series of slides presented on the monitor, and their eye positions were recorded. The eye positions were segmented into fixations that are linked to the displayed images.⁵⁶ VAST is composed of various oculomotor function assessments; however, for the purpose of this study, we exclusively evaluated the SPS task. In this task, the participants were instructed to alternate the gaze between two stationary targets ($\pm 10^\circ$ off-center in the horizontal dimension) as many times as possible in 40 sec. The outcome measure was the number of SPSs executed during this 40-sec time period. The number of SPSs executed in the first, second, third, and fourth 10-sec sub-intervals also were recorded. To compare our results with what has been reported in other studies, we also calculated the number of SPSs executed in the first 30-sec sub-interval.

Neuroimaging acquisition

All participants underwent MRI with a 3T MRI system (Signa HDx; GE Healthcare, Milwaukee, WI) using a standard 8-channel head coil to obtain structural and diffusion-weighted imaging (DWI). A high-resolution T1-weighted whole-brain scan was acquired using inversion recovery fast spoiled gradient echo sequence with the following parameters: 180 axial slices with 1 mm thickness; 3-msec echo time (TE); 7.8-ms repetition time (TR); 450-msec inversion time; 15 flip angle; 20-cm field of view (FOV); 200×200 matrix size; $1 \times 1 \times 1 \text{ mm}^3$ voxel size.

One DWI scan was obtained with diffusion gradients applied across 60 spatial directions ($b = 1000 \text{ sec/mm}^2$), as well as 10 non-diffusion weighted (B_0) scans. The DWI had the following parameters: 2.4 mm thick axial slices, TR = 17,000 msec, FOV = 23 cm, 96×96 matrix size, $2.4 \times 2.4 \text{ mm}^2$ in-plane resolution.

DTI processing

DTI processing was performed using Functional MRI of the Brain Software Library (FSL, v.5.0.9; www.fmrib.ox.ac.uk/fsl).⁵⁷ Preprocessing included the following steps: 1) Diffusion weighted images were corrected for eddy current and motion artefact with FSL Diffusion Toolbox⁵⁸; 2) Both T1-weighted and diffusion-weighted images were skull-stripped using the Brain Extraction Tool⁵⁹; 3) Using DTIFit in the Diffusion Toolbox, the preprocessed images were fit with a diffusion tensor model at each voxel to obtain fractional anisotropy (FA), mean diffusivity (MD), based on the three eigenvalues (λ_1 , λ_2 , and λ_3). Axial diffusivity (AD) and radial diffusivity (RD) were calculated as λ_1 , and $(\lambda_2 + \lambda_3)/2$, respectively.

Region of interest definition

To reconstruct specific WM tracts, we used probabilistic DTI tractography. We defined distinct seed regions (a region of interest [ROI] consisting of a few voxels in native diffusion space of each brain) for the following tracts: right and left superior longitudinal fasciculi (SLF); right and left uncinate fasciculi (UF); right and left cingulum tracts (Cg); and corpus callosum (CC). The ROIs were drawn manually on coronal, axial, and sagittal slices through which all or most fibers of these tracts pass.⁶⁰ Exclusion masks also were employed to prevent interference from neighboring tract fibers. The ROIs for each tract were drawn on the FA and color-coded maps as follows (Fig. 1):

- a. SLF: The seed ROI was placed on the coronal slice posterior to the postcentral gyrus.^{60,61} The exclusion masks were drawn on the internal and external capsule to exclude

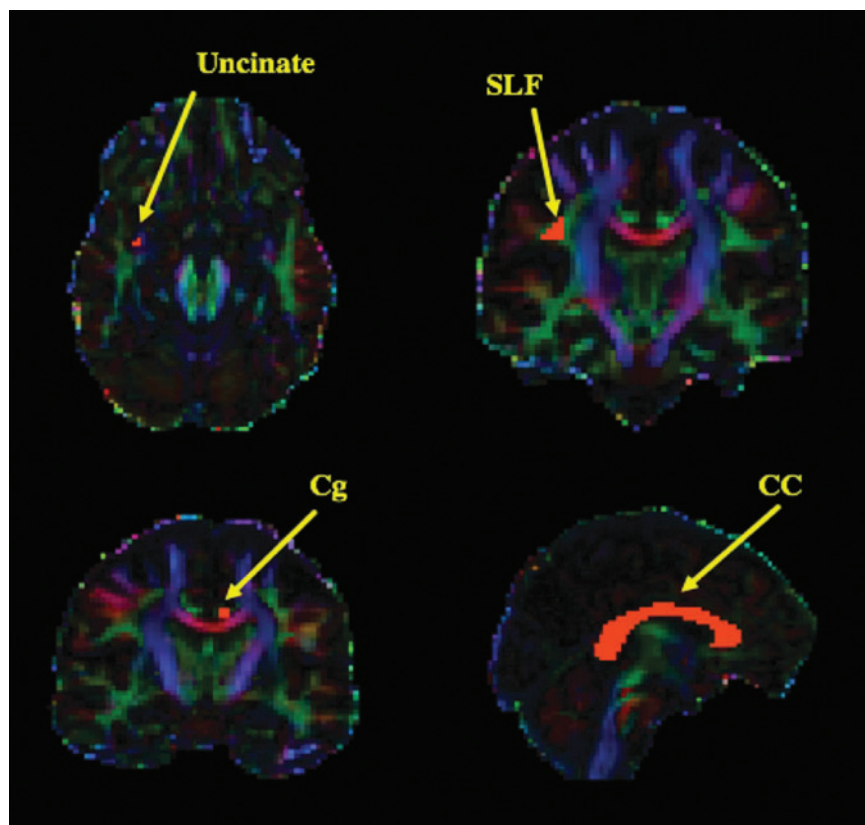


FIG. 1. Seed placement for tractography of four white matter tracts. Probabilistic tractography methods were used to perform fiber tracking: Seeds localized where the tracts are known to pass through a bottleneck. SLF: superior longitudinal fasciculus; Cg: cingulum bundle; CC: corpus callosum.

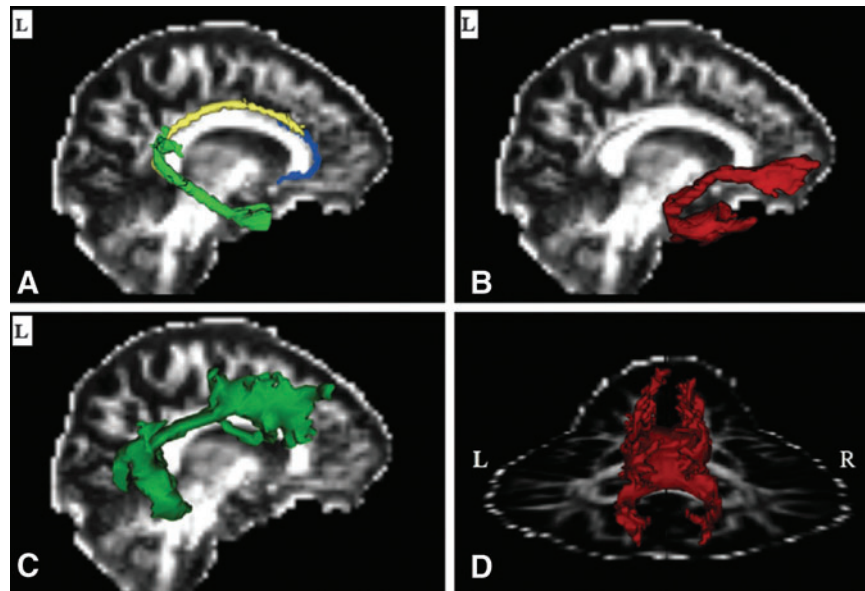


FIG. 2. Tractography of the white matter tracts for a single patient. (A) Cingulum bundle: blue: subgenual subcomponent, yellow: body or retrosplenial subcomponent, green: parahippocampal subcomponent; (B) Uncinate fasciculus; (C) Superior longitudinal fasciculus; (D) Corpus callosum.

fibers of the corona radiata, and on the inferior longitudinal fasciculus (ILF).

- b. UF: The seed ROI was placed on axial cuts, at the area of transition (purple on color-coded map) from the orbitofrontal cortex to the anterior temporal lobe.⁶⁰ Two exclusion masks were drawn on the midline sagittal view and on the coronal view to remove commissural fibers and ILF fibers, respectively.
- c. Cg: The seed ROI was placed on the coronal slice, at the mid-way point between the back of the genu and the front of the splenium.³⁴ An exclusion mask was drawn on the midline sagittal view to exclude commissural fibers.
- d. CC: The seed ROI was placed on the midsagittal slice to define the whole CC tract.⁶² An exclusion mask was drawn on the axial plane, superior to the midbrain, to remove projection fibers going to the brainstem.

Fiber tracking

Using the FSL Bayesian estimation of diffusion parameters (Bedpostx) and Protrackx tool, probabilistic tractography was performed.⁶³ Fiber tracking from each voxel within each seed ROI using a step length of 0.5 cm and curvature of 0.2 generated 5000 streamline samples. This process was run separately for each tract in the right and left hemispheres. The outcome was a probabilistic map of the connections between the voxels in the seed ROI to the rest of the brain. For each resultant tract, the number of streamlined samples in the voxels in the tract maps was divided by the total number of streamlined samples that were not rejected from the exclusion masks (waytotal), to normalize the tractography maps. Normalization was necessary since each tractography map might have been generated from a seed ROI with a different number of voxels.^{4,60} The obtained tract maps for Cg and UF were thresholded to a value equal to 20% of the 95th percentile of the intensity values' distribution in the voxels in the tract. A threshold of 40% for the same process was used for the resultant CC and SLF tracts.^{4,60} This thresholding step was performed to take into account the possible differences between the tracts, as well as background noise.⁶⁰ We chose a higher threshold value for the SLF and CC to

normalize for the larger number of starting seeds that were used for these tracts, compared with that of the Cg and UF. The thresholded tract maps were then binarized for each participant and were used to mask the participant's FA, AD, RD, and MD brain

TABLE 1. PARTICIPANTS CHARACTERISTICS (MEAN \pm STANDARD DEVIATION)

<i>N</i>	59
Sex (female/male)	21/38
Age (years)	33.37 \pm 13.9
Years of education	14.7 \pm 2.3
Number of concussions	4.0 \pm 2.0 (minimum = 2; maximum = 10)
Total number of symptoms	27.1 \pm 12.3
Interval between last concussion and testing (months)	25.9 \pm 63.6 (Median = 12.0; minimum = 1.0, maximum = 468)
Total number of SPSs performed in 40 sec	79 \pm 18.7
Number of SPSs in 1st 10-sec interval	21.8 \pm 6.0
Number of SPSs in 2nd 10-sec interval	20.1 \pm 4.8
Number of SPSs in 3rd 10-sec interval	19.0 \pm 5.0
Number of SPSs in 4th 10-sec interval	18.2 \pm 4.8
Corpus callosum FA	0.494 \pm 0.022
Corpus callosum MD	0.000898 \pm 0.000034
Right uncinate fasciculus FA	0.357 \pm 0.027
Right uncinate fasciculus MD	0.000896 \pm 0.000036
Left uncinate fasciculus FA	0.340 \pm 0.028
Left uncinate fasciculus MD	0.000880 \pm 0.000040
Right cingulum tract FA	0.340 \pm 0.028
Right cingulum tract MD	0.000877 \pm 0.000037
Left cingulum tract FA	0.352 \pm 0.031
Left cingulum tract MD	0.000873 \pm 0.000036
Right superior longitudinal fasciculus FA	0.389 \pm 0.024
Right superior longitudinal fasciculus MD	0.00814 \pm 0.000027
Left superior longitudinal fasciculus FA	0.391 \pm 0.024
Left superior longitudinal fasciculus MD	0.000809 \pm 0.000032

SPS, self-paced saccade; FA, fractional anisotropy; MD, mean diffusivity.

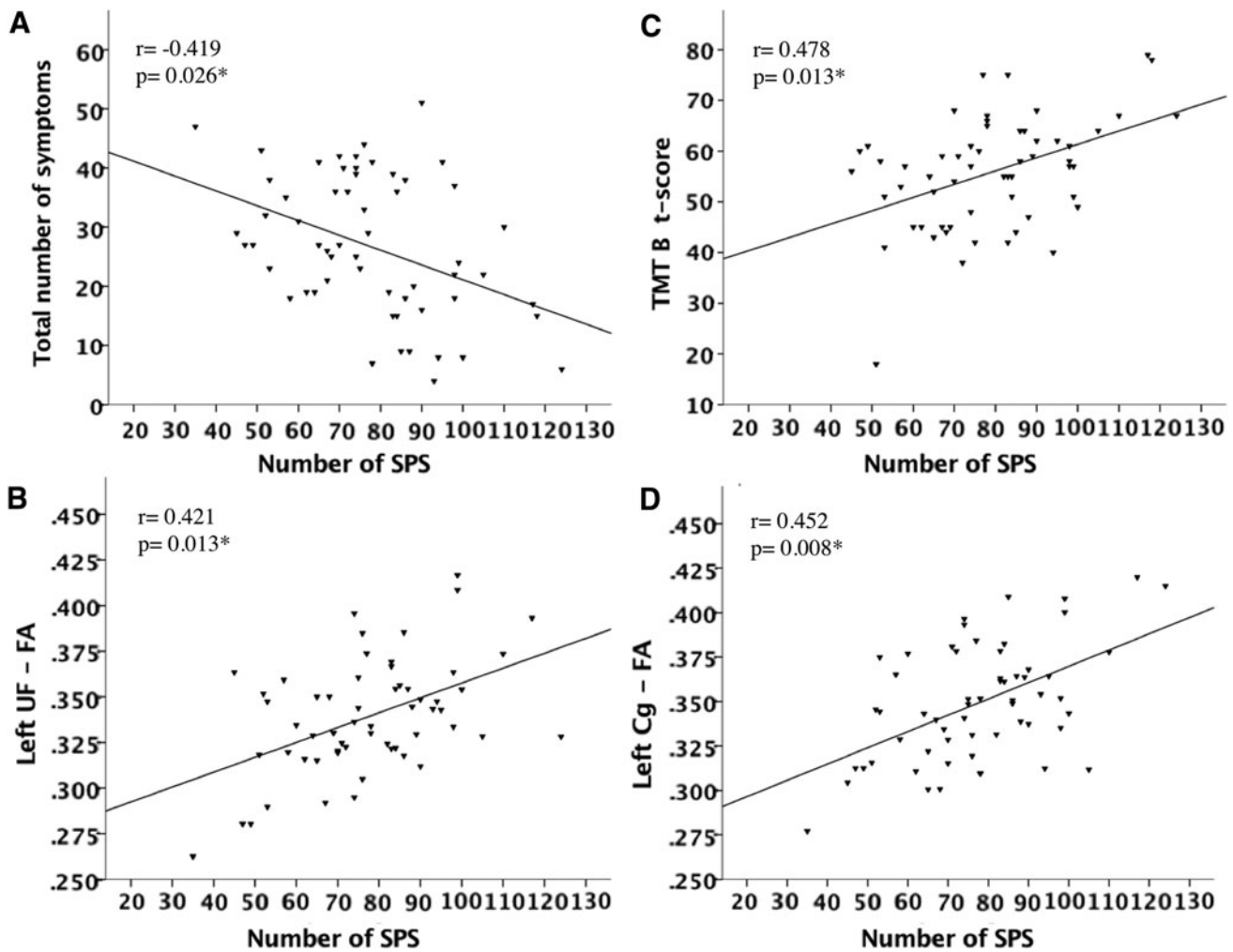


FIG. 3. Correlations with the number of self-paced saccades (SPSs). *Bonferroni-adjusted p value, significant at $p < 0.05$; controlled for age and sex. (A) Number of SPS was negatively correlated with total number of concussion related symptoms; (B) positive association between the number of SPS with the fractional anisotropy (FA) of left uncinate fasciculus (UF); (C) t-score obtained in Trail Making Test Part B was associated with the performance of patients in SPS task; (D) positive association between the number of SPS with the FA of left Cg.

maps. Finally, the FA, MD, AD, and RD of each tract was calculated by taking the average of the values among the identified voxels. An example of the tract reconstructions for a single patient is shown in Figure 2.

Tract partitioning

CC partitioning. We divided the CC into five distinct segments, as outlined by Hofer and Frahm⁶² which consisted of fibers projecting to: 1) prefrontal; 2) premotor and supplementary motor; 3) primary motor; 4) primary sensory; and 5) communication fibers of parietal, temporal, and occipital cortical areas.

Cg bundle partitioning. The Cg is also a long tract, connecting regions in prefrontal, parietal, and temporal lobes.^{33,64} The Cg is composed of association fibers of different lengths. Therefore, it is likely that by defining only one inclusion ROI for the Cg tractography, we might miss many short fibers that do not pass through the ROI mentioned above. In addition, due to its various length of the fibers, different parts of Cg are likely to be responsible for different underlying functions.³⁵ To address this issue, we applied the same approach proposed by Jones and colleagues³⁴ to draw inclusion ROIs at different regions along the Cg path. This approach also enabled us to reconstruct three dis-

tinct Cg subcomponents: subgenual, retrosplenial, and parahippocampal subdivisions.

ROIs and reconstructed tracts verification

Tractography and partitioning of all tracts was performed by F.T or S.I, and all were visually assessed and confirmed by an experienced neurologist M.C.T.

Statistical analysis

Statistical analyses were conducted using SPSS software (SPSS Inc. v. 24). First, a series of Pearson partial correlations were carried out to determine whether there was an association between the number of SPSs with: i) the number of self-reported concussions; ii) the number of self-reported symptoms; iii) the FA values of WM tracts (Right and left SLF, UF, and Cg, as well as CC); iv) neuropsychological parameters; and v) the log of the interval between last concussion and testing while controlling for age and gender. We used a log transformed "interval between last concussion and testing" variable for our analyses to correct for the skewed distribution. The two-tailed level of significance was set at $\alpha = 0.05$. Bonferroni adjustments were applied to account for multiple comparisons (comparisons between the number of SPSs and the parameters [i-v] listed above). All the p values reported are adjusted

TABLE 2. CORRELATION BETWEEN NUMBER OF SPSs WITH DTI PARAMETERS OF WM INTEGRITY

	<i>r</i>	<i>Unadjusted p</i>	<i>Adjusted p*</i>
Corpus callosum			
FA	0.188	0.17	N.S.
MD	-0.264	0.05	N.S.
Superior longitudinal fasciculus			
<i>Right</i>			
FA	0.063	0.65	N.S.
MD	-0.122	0.36	N.S.
<i>Left</i>			
FA	0.118	0.39	N.S.
MD	-0.105	0.44	N.S.
Uncinate fasciculus			
<i>Right</i>			
FA	0.023	0.86	N.S.
MD	-0.75	0.58	N.S.
[†] <i>Left</i>			
FA	0.421	0.001	0.013
MD	-0.432	0.001	0.013
AD	-0.166	0.22	N.S.
RD	-0.474	<0.001	0.004
Cingulum tract			
<i>Right</i>			
FA	0.177	0.19	N.S.
MD	-0.83	0.54	N.S.
[†] <i>Left</i>			
FA	0.452	<0.001	0.008
MD	-0.322	0.016	0.20
AD	0.014	0.92	N.S.
RD	-0.404	0.002	0.026

Pearson partial correlation, controlled for age and gender.

*Bonferroni adjusted *p* value, significant at <0.05.

[†]To minimize type II error, AD and RD values measured only for the tracts with statistically significant correlation between their FA and number of SPS.

SPS, self-paced saccade; DTI, diffusion tensor imaging; WM, white matter; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity, N.S., not significant (adjusted *p*>0.1).

for multiple comparisons unless otherwise stated. To minimize the number of comparisons and hence type II statistical error, when applicable, we only ran partial correlation analyses (controlled for age and gender) between the number of SPSs with subcomponents of the partitioned tracts that showed significant correlations with SPS in the previous step. Bonferroni correction for multiple comparisons was applied accordingly.

Finally, we carried out mediation analyses to explore the potential mediation effect of specific WM tracts on the relationship between each of “log of interval between last concussion and testing” or “total number of symptoms” and the “number of SPSs.” To do so, we used the SPSS macro PROCESS tool⁶⁵ which is implemented in SPSS version 24. We estimated the total, direct, and indirect effects, as well as their associated standard error (SE) and 95% confidence intervals (CI; while controlling for age) using the 5000 bootstrap samples.^{65,66} Mediation ratio also was calculated for each model as the ratio of direct effect to the total effect.⁶⁷ All mediation analyses adjusted for participants’ age. For each specific effect, if the interval did not contain zero, it was considered statistically significant.

Results

Participant profile

Table 1 summarizes participants’ demographic information. Mechanism of injury for the participants were as follows: only sport

TABLE 3. CORRELATION BETWEEN NUMBER OF SPS WITH FA VALUES OF CINGULUM AND CORPUS CALLOSUM SUBCOMPONENTS

	<i>r</i>	<i>Unadjusted p</i>	<i>Adjusted p*</i>
Left cingulum tract FA			
<i>Subgenual</i>	0.386	0.003	0.009
<i>Body</i>	-0.014	0.918	1.000
<i>Parahippocampal</i>	0.311	0.02	0.06
Right cingulum tract FA			
<i>Subgenual</i>	0.073	0.598	1.000
<i>Body</i>	-0.098	0.479	1.000
<i>Parahippocampal</i>	0.149	0.284	1.000
Corpus callosum FA			
1	0.211	0.126	0.630
2	0.341	0.012	0.060
3	0.242	0.078	0.390
4	0.241	0.079	0.395
5	0.031	0.826	1.000

Pearson partial correlation, controlled for age and gender.

*Bonferroni adjusted *p* value; significant at *p*<0.05 (Bonferroni correction).

SPS, self-paced saccade; FA, fractional anisotropy.

(24 patients), only motor vehicle accidents (MVA; 2 participants), mixed mechanisms (e.g., sport, fall, fight, MVA; 33 participants). All participants completed the SPS assessment (i.e., 40 sec) with a mean±SD for number and amplitude of 79.0±18.7 and 20.1°±0.61°, respectively. Number of SPSs executed in the first 30-sec sub-interval calculated as 60.8±14.4.

SPS and concussion profile

There was no significant relationship between the number of SPSs with the self-reported number of concussions (*r*=-0.064, *p*=1.00). However, a significant negative correlation was observed between the number of SPSs with the total number of symptoms (*r*=-0.419, *p*=0.026; Fig. 3A).

The significant correlation with the total number of concussion symptoms led us to examine the relationship between the number of SPSs with each symptom domain separately. Symptoms in three domains showed a significant association with the number of SPSs: executive function, behavioral, and constitutional symptoms, (*r*=-0.441, *p*=0.013; *r*=-0.422, *p*=0.013; and *r*=-0.400, *p*=0.013, respectively). The Pearson partial correlation of the SPSs and the log of the interval between last concussion and testing also showed that participants who were concussion-free for longer periods had a higher number of SPSs (*r*=0.471, *p*=0.005).

SPS and neuropsychological parameters

We found a significant positive correlation between the number of SPSs and the TMT-B t-score (*r*=0.478, *p*=0.013; Fig. 3C), whereas there was no significant association between the number of SPSs and the TMT-A t-score (*r*=0.257, *p*=0.91) or the DS-backward percentile score (*r*=0.235, *p*=0.12). A trend towards a significant relationship was observed between the number of SPSs and the VS-backward scaled score (*r*=0.385, *p*=0.065).

SPS and WM integrity of the selected tracts

Table 2 shows detailed results of partial correlation between the number of SPSs with DTI parameters of SLF, UF, Cg, and CC tracts while controlling for age and gender (Supplementary Fig. 1; see

TABLE 4. PARAMETERS OF MEDIATION ANALYSES

	Whole model			Paths					
	R ²	F	p*	β/effect	SE	t	p*	95% CI	
Model a	0.278	6.42	< 0.001	Total effect (path c)	-0.622	0.192	-3.25	0.002	-1.00_ -0.24
				Direct effect (path c')	-0.423	0.195	-2.17	0.035	-0.81_ -0.03
				Indirect effect	-0.199	0.098			-0.45_ -0.052
				†Ratio of indirect to total effect	0.320	0.243			0.10_0.79
				Path a	-0.002	0.0005	-2.90	0.006	-0.0025_ -0.0005
				Path b	132.7	48.8	2.72	0.009	34.60_230.7
Model b	0.330	8.21	< 0.001	Total effect (path c)	-0.622	0.192	-3.25	0.002	-1.00_ -0.24
				Direct effect (path c')	-0.563	0.175	-3.22	0.002	-0.91_ -0.21
				Indirect effect	-0.060	0.082			-0.27_0.07
				†Ratio of indirect to total effect	0.096	0.348			-0.15_0.42
				Path a	-0.0002	0.0003	-0.711	0.48	-0.0009_0.0004
				Path b	248.1	72.1	3.44	0.0012	103.2_392.9
Model c	0.338	9.20	< 0.001	Total effect (path c)	15.29	5.1	3.00	0.004	5.10_25.5
				Direct effect (path c')	14.44	4.51	3.20	0.002	5.39_23.5
				Indirect effect	0.86	2.29			-3.67_5.52
				†Ratio of indirect to total effect	0.056	1.28			-0.37_0.49
				Path a	0.006	0.016	0.35	0.726	-0.026_0.037
				Path b	154.0	38.4	4.01	<0.001	77.0_231.1
Model d	0.259	6.29	0.001	Total effect (path c)	15.29	5.1	3.00	0.004	5.10_25.5
				Direct effect (path c')	10.21	5.1	2.01	0.05	0.032_20.38
				Indirect effect	5.09	2.51			0.981_10.83
				†Ratio of indirect to total effect	0.333	1.0			0.06_1.1
				Path a	0.024	0.009	2.70	0.009	0.0061_0.0409
				Path b	216.5	73.89	2.93	0.005	68.32_364.6

†Mediation ratio.

*In all mediation analyses, age considered as a covariate.

β, beta coefficient; SE, standard error; CI, confidence interval; path c, total effect of the independent variable (i.e., total number of symptoms or log of interval from last concussion) on the dependent variable (i.e., number of self-paced saccades); path c', direct effect of the independent variable on the dependent variable; path a, effect of the independent variable on the mediator (i.e., left subgenual cingulum fractional anisotropy, or left uncinate fasciculus fractional anisotropy); path b, effect of the mediator on the dependent variable.

online supplementary material at <http://www.liebertpub.com>). The number of SPSs was correlated with the parameters of only two of the tracts: left UF (Fig. 3B), and left Cg (Fig. 3D). To minimize the risk of statistical type II error, correlations with AD and RD values were calculated only for these two tracts while FA and MD were calculated for all the tracts. As is shown in Table 3, the FA of the subgenual subcomponent was the only part of the left Cg that demonstrated a significant positive correlation with the number of SPSs after Bonferroni adjustment.

Mediation analyses

The results from the mediator models are presented in Figure 4 and Table 4. As shown in Figure 4, the left subgenual Cg FA and left UF FA were entered into separate mediator models to test the hypothesis that the WM tracts mediate the relationship between the number of SPSs and the number of symptoms (Fig. 4A, 4B) and the interval from last concussion (Fig. 4C, 4D) with number of SPSs. Left subgenual Cg FA significantly and partially mediated the effects of the total number of symptoms on the number of SPSs (indirect effect=-0.199, SE=0.098, 95% CI=-0.45 - -0.052; mediation ratio=0.320, SE=0.243, 95% CI=0.10 - 0.79; Fig. 4A), while left UF FA showed no significant mediating effect on this relationship (indirect effect=-0.06, SE=0.082, 95%

CI=-0.27 - 0.07; Fig. 4B). In contrast, an indirect effect of the log of interval from last concussion on the number of SPSs via left UF FA was statistically significant (indirect effect=5.09, SE=2.51, 95% CI=0.98 - 10.8; mediation ratio=0.333, SE=1.0, 95% CI=0.06 - 1.1; Fig. 4D). However, no significant mediating effect was found for the left subgenual Cg FA (indirect effect=0.86, SE=2.29, 95% CI=-3.67 - 5.52; Fig. 4C).

Discussion

Our results indicated that number of SPS eye movement was associated with number of concussion symptoms, interval since last concussion, and integrity of two major WM tracts, the left UF and left Cg. Moreover, the association between the number of SPSs and number of concussion symptoms was mediated through the integrity of the left subgenual Cg, while the association between number of SPSs and interval from last concussion was mediated through the integrity of the left UF.

SPS tasks have been conducted differently in most studies.⁶⁸ Therefore, it is not easy to compare the number of SPSs, which the PCS patients performed in our oculomotor function test, with the performance of either PCS patients or healthy individuals in other studies. However, results from some of the studies that used a similar SPS task have shown that healthy individuals are able to

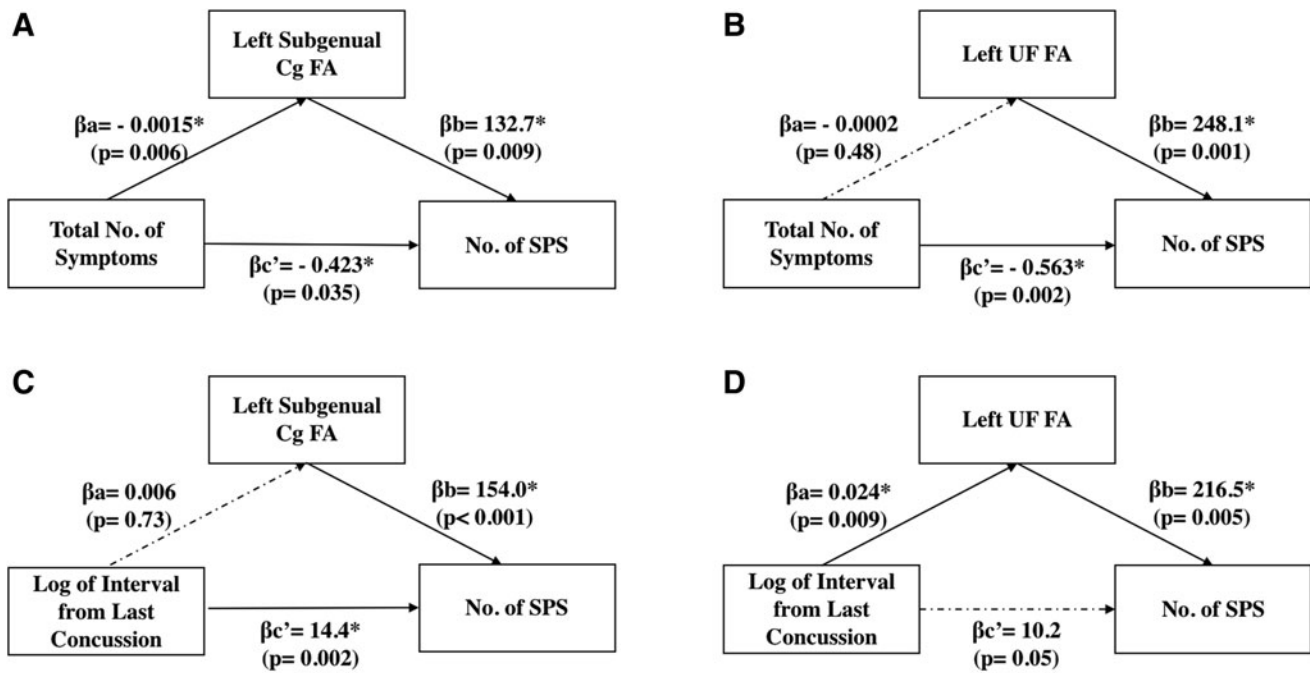


FIG. 4. Mediation models for number of self-paced saccades (SPSs). *Statistically significant at the level of $p < 0.05$. (A) and (B): integrity of the left subgenual cingulum (Cg) tract mediates the relationship between the number of symptoms and number of SPS; (C) and (D): integrity of the left uncinate fasciculus (UF) tract mediates the relationship between the log of interval from last concussion and the number of SPS. β_c' , direct effect of the independent variable (i.e., total number of symptoms or log of interval from last concussion) on the dependent variable (i.e., number of SPSs); β_a , effect of the independent variable on the mediator (i.e., left subgenual Cg fractional anisotropy [FA], or left UF FA); β_b , effect of the mediator on the dependent variable.

perform an average of 74 to 84 SPSs in 30 sec.^{69–71} The mean number of SPSs that the patients in our study performed in the first 30 sec (i.e., 60.8 ± 14.4) appears lower than what is reported for the healthy controls in these studies.

We found that the number of SPSs that a patient could perform in the task is negatively correlated with the number of symptoms reported in three domains: executive function, behavioral, and constitutional symptoms. These domains include the symptoms that commonly persist after a concussion, such as difficulty concentrating, fatigue, dizziness or feeling in a fog, sensitivity to light and/or noise, depression, and anxiety.^{1,39} This finding also is consistent with the previous observation that increased number of symptoms in patients with PCS may significantly influence several aspects of their performance on the SPS task, such as number, inter-saccadic interval, and duration of the saccades.⁷

In addition to the subjective executive symptoms reported by patients, we found a significant association between the number of SPSs and TMT-B, and a trend toward significance with VS-backward—both conventional neuropsychological tests of executive function. Interestingly, previous studies have shown the limited ability of neuropsychological assessments to detect the brain impairment in patients with PCS.^{7,13} A study published recently⁷² indicated that saccades could be more useful in reflecting chronic effects of concussion than many of the conventional neuropsychological tests, including TMT-B. However, the significant association between the performance on TMT-B and SPS tasks may indicate an overlap in the brain regions required to perform both tasks.⁷³

Our findings of correlations between the number of SPSs and microstructural integrity only in the left UF and left Cg tracts re-

inforce results from previous studies that reported hemispheric asymmetry in controlling saccades.^{74–76} Transcranial magnetic stimulation and lesion studies have shown that the SEF, particularly in the left hemisphere, is crucial in learning and controlling saccades.⁷⁷ Similarly, structural and functional asymmetry in the Cg and the UF has been widely studied.^{37,78–80} Hemispheric dominance in other regions of the brain, such as the ACC, are not as well understood.²⁶

Most studies of DTI in PCS have focused only on the FA changes and few have reported MD, AD, and/or RD values in WM tracts.⁸¹ However, our findings of negative correlations between MD and RD (and not AD) of the left UF and the left Cg with the number of SPSs (Table 2) are consistent with the few previous studies that have reported the pattern of decreased FA and increased MD and RD in different WM tracts of PCS patients.^{5,27,28} As is shown in some studies, increased RD is more suggestive of myelin degeneration, whereas AD is usually increased in WM tracts due to axonal pathology.^{82–84}

Within the left Cg, the subgenual subcomponent was best correlated with number of SPSs. The subgenual Cg has been identified as a target for deep brain stimulation in the treatment of depression.^{85,86} Moreover, it has been shown that the anterior cingulum FA values in patients with depression correlate with their cognitive performance, particularly on tasks of planning and attention.⁸⁷

The association between SPS performance and the integrity of the left UF and subgenual Cg tracts that we found in patients with PCS also may exist in healthy people without a history of concussion. However, the results from our mediation analyses (Fig. 4A, 4B) suggest that the left subgenual Cg tract explains approximately 32% of the concussion symptoms reported by patients. In addition, as mentioned above, the correlation results revealed significant

associations between the number of SPSs and the number of concussion symptoms. Hence, taken together, we can conclude that apart from individual variability in making SPSs that also might be seen in healthy people with no history of concussion, this task is sensitive to disruption in the WM integrity that can be caused by concussions.

The UF and Cg tracts are among the commonly affected tracts in patients with PCS.^{5,88} However, in general, the DTI literature on patients with PCS contains conflicting results. Some studies have reported associations between cognitive deficits in PCS and reduced integrity of WM tracts,^{89–91} while others have failed to replicate these results.⁹² This discrepancy in the concussion literature is likely to be caused by both the heterogeneous nature of concussion and methodological inconsistencies (e.g., participants' age and gender, number of concussions, interval between last concussion and testing, definition of concussion and PCS, and the neuroimaging approach used). We tried to minimize the confounding factors by using partial correlation and controlling for important factors such as age and gender.

Our results also revealed that the PCS patients who had experienced their last concussion more recently tended to generate fewer SPSs. Interestingly, our mediation analyses clearly showed that this relationship is mediated only by the integrity of the left UF tract (Fig. 4D) and not the subgenual Cg tract integrity (Fig. 4C). This finding suggests that there may be a differential healing process in different WM tracts that are involved in controlling and generating SPSs. In other words, although both the left subgenual Cg and left UF play roles in the performance of the SPS task in PCS patients, the tracts do not contribute in the same way to the performance of the SPS and so alteration of integrity of a specific tract leads to different outcomes: decreased FA in the subgenual Cg is associated with a higher number of symptoms and a lower number of SPSs (model a), while longer interval from last concussion is associated with a greater integrity only in the left UF and not in the left subgenual Cg, and thus no change in the number of symptoms (model c and d). Taken together, the results suggest that the number of SPSs might be considered as a biomarker of recovery that may reflect the ongoing healing process of patients with PCS. However, to investigate whether this oculomotor function test can serve as a suitable recovery biomarker, longitudinal studies are required.⁶⁸

An important point regarding methodology that needs to be considered is that many previous studies using DTI in concussed patients have mainly applied voxel-based methods such as tract-based spatial statistics (TBSS).^{31,90,93} In this study, we used the probabilistic tractography approach and manually drew ROIs for each participant. This method let us take advantage of *in vivo* dissection and accurately evaluate WM microstructure of the entire tract while accounting for the inherent variability of brain morphology. This is in contrast to the TBSS method that restricts WM tracts to core (skeleton voxels) WM structures.^{94,95}

Our study has a number of limitations. The most important being the lack of a control group to compare the performance on the SPS task between healthy individuals and PCS patients. Another limitation of this study was that we sought an association of SPSs with seven major WM tracts (i.e., CC, and SLF, UF, and Cg at each side) that previously were shown to be involved in visual perception; however, other WM tracts, even though less likely, also might be associated with performance of SPS. Further, we only measured the number of SPSs but other measurements such as average or peak velocity of the saccades might also provide some information and should be investigated in PCS patients. Therefore, more studies with a control group and larger patient sample size with more comprehensive oculomotor measures are required to confirm and extend the results of this study.

In conclusion, our findings indicate that the number of SPSs, a simple objective tool, correlates with subjective symptom burden reported by patients with PCS as well as their performance on certain neuropsychological tests of executive function. Our results also show a relationship between their performance on the SPS task to the microstructural integrity of their left UF and Cg tracts. This simple oculomotor task may provide clinicians and researchers an objective tool for monitoring the recovery of patients suffering from post-concussion symptoms.

Author Disclosure Statement

Moshe Eizenman is a director at EI-MAR Inc., Toronto, Ontario. No competing financial interests exist.

References

- Ryan, L.M. and Warden, D.L. (2003). Post concussion syndrome. *Int. Rev. Psychiatry* 15, 310–316.
- McCrea, M., Guskiewicz, K., Randolph, C., Barr, W.B., Hammeke, T.A., Marshall, S.W., Powell, M.R., Ahn, K.W., Wang, Y., and Kelly, J.P. (2013). Incidence, clinical course, and predictors of prolonged recovery time following sport-related concussion in high school and college athletes. *J. Int. Neuropsychol. Soc.* 19, 22–33.
- Gardner, A., Kay-Lambkin, F., Stanwell, P., Donnelly, J., Williams, W.H., Hiles, A., Schofield, P., Levi, C., and Jones, D.K. (2012). A systematic review of diffusion tensor imaging findings in sports-related concussion. *J. Neurotrauma* 29, 2521–2538.
- Goswami, R., Dufort, P., Tartaglia, M., Green, R., Crawley, A., Tator, C., Wennberg, R., Mikulis, D., Keightley, M., and Davis, K.D. (2016). Frontotemporal correlates of impulsivity and machine learning in retired professional athletes with a history of multiple concussions. *Brain Struct. Funct.* 221, 1911–1925.
- Asken, B.M., DeKosky, S.T., Clugston, J.R., Jaffee, M.S., and Bauer, R.M. (2017). Diffusion tensor imaging (DTI) findings in adult civilian, military, and sport-related mild traumatic brain injury (mTBI): a systematic critical review. *Brain Imaging Behav.* 2017 Mar 24; Epub ahead of print.
- Bazarian, J.J., Zhong, J., Blyth, B., Zhu, T., Kavcic, V., and Peterson, D. (2007). Diffusion tensor imaging detects clinically important axonal damage after mild traumatic brain injury: a pilot study. *J. Neurotrauma* 24, 1447–1459.
- Heitger, M.H., Jones, R.D., Macleod, A., Snell, D.L., Frampton, C.M., and Anderson, T.J. (2009). Impaired eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability. *Brain* 132(Pt 10), 2850–2870.
- Collie, A., Darby, D., and Maruff, P. (2001). Computerised cognitive assessment of athletes with sports related head injury. *Br. J. Sports Med.* 35, 297–302.
- Collie, A., Maruff, P., McStephen, M., and Darby, D. (2003). Psychometric issues associated with computerised neuropsychological assessment of concussed athletes. *Br. J. Sports Med.* 37, 556–559.
- Lovell, M.R. (2002). The relevance of neuropsychologic testing for sports-related head injuries. *Curr. Sports Med. Rep.* 1, 7–11.
- Binder, L.M., Rohling, M.L., and Larrabee, G.J. (1997). A review of mild head trauma. Part I: Meta-analytic review of neuropsychological studies. *J. Clin. Exp. Neuropsychol.* 19, 421–431.
- Schretlen, D.J. and Shapiro, A.M. (2003). A quantitative review of the effects of traumatic brain injury on cognitive functioning. *Int. Rev. Psychiatry* 15, 341–349.
- Iverson, G.L. (2005). Outcome from mild traumatic brain injury. *Curr. Opin. Psychiatry* 18, 301–317.
- Suchoff, I.B., Kapoor, N., Waxman, R., and Ference, W. (1999). The occurrence of ocular and visual dysfunctions in an acquired brain-injured patient sample. *J. Am. Optom. Assoc.* 70, 301–308.
- Brahm, K.D., Wilgenburg, H.M., Kirby, J., Ingalla, S., Chang, C.Y., and Goodrich, G.L. (2009). Visual impairment and dysfunction in combat-injured servicemembers with traumatic brain injury. *Optom. Vis. Sci.* 86, 817–825.
- Goodrich, G.L., Flyg, H.M., Kirby, J.E., Chang, C.Y., and Martinsen, G.L. (2013). Mechanisms of TBI and visual consequences in military and veteran populations. *Optom. Vis. Sci.* 90, 105–112.

17. Master, C.L., Scheiman, M., Gallaway, M., Goodman, A., Robinson, R.L., Master, S.R., and Grady, M.F. (2016). Vision diagnoses are common after concussion in adolescents. *Clin. Pediatr. (Phila.)* 55, 260–267.
18. Cifu, D.X., Wares, J.R., Hoke, K.W., Wetzel, P.A., Gitchel, G., and Carne, W. (2015). Differential eye movements in mild traumatic brain injury versus normal controls. *J. Head Trauma Rehabil.* 30, 21–28.
19. Tyler, C.W., Likova, L.T., Mineff, K.N., and Nicholas, S.C. (2015). Deficits in the activation of human oculomotor nuclei in chronic traumatic brain injury. *Front. Neurol.* 6.
20. McDowell, J.E., Dyckman, K.A., Austin, B.P., and Clementz, B.A. (2008). Neurophysiology and neuroanatomy of reflexive and volitional saccades: evidence from studies of humans. *Brain Cogn.* 68, 255–270.
21. Ro, T., Henik, A., Machado, L., and Rafal, R.D. (1997). Transcranial magnetic stimulation of the prefrontal cortex delays contralateral endogenous saccades. *J. Cogn. Neurosci.* 9, 433–440.
22. Müri, R.M. and Nyffeler, T. (2008). Neurophysiology and neuroanatomy of reflexive and volitional saccades as revealed by lesion studies with neurological patients and transcranial magnetic stimulation (TMS). *Brain Cogn.* 68, 284–292.
23. Gaymard, B., Rivaud, S., and Pierrot-Deseilligny, C. (1993). Role of the left and right supplementary motor areas in memory-guided saccade sequences. *Ann. Neurol.* 34, 404–406.
24. Muri, R.M., Vermersch, A.-I., Rivaud, S., Gaymard, B., and Pierrot-Deseilligny, C. (1996). Effects of single-pulse transcranial magnetic stimulation over the prefrontal and posterior parietal cortices during memory-guided saccades in humans. *J. Neurophysiol.* 76, 2102–2106.
25. Miyauchi, S., Misaki, M., Kan, S., Fukunaga, T., and Koike, T. (2009). Human brain activity time-locked to rapid eye movements during REM sleep. *Exp. Brain Res.* 192, 657–667.
26. Gaymard, B., Rivaud, S., Cassarini, J., Dubard, T., Rancurel, G., Agid, Y., and Pierrot-Deseilligny, C. (1998). Effects of anterior cingulate cortex lesions on ocular saccades in humans. *Exp. Brain Res.* 120, 173–183.
27. Bartnik-Olson, B.L., Holshouser, B., Wang, H., Grube, M., Tong, K., Wong, V., and Ashwal, S. (2014). Impaired neurovascular unit function contributes to persistent symptoms after concussion: a pilot study. *J. Neurotrauma* 31, 1497–1506.
28. Polak, P., Leddy, J.J., Dwyer, M.G., Willer, B., and Zivadinov, R. (2015). Diffusion tensor imaging alterations in patients with post-concussion syndrome undergoing exercise treatment: a pilot longitudinal study. *J. Head Trauma Rehabil.* 30, E32–E42.
29. Dean, P.J., Sato, J.R., Vieira, G., McNamara, A., and Sterr, A. (2015). Long-term structural changes after mTBI and their relation to post-concussion symptoms. *Brain Inj.* 29, 1211–1218.
30. Levin, H.S., Wilde, E., Troyanskaya, M., Petersen, N.J., Scheibel, R., Newsome, M., Radaideh, M., Wu, T., Yallampalli, R., and Chu, Z. (2010). Diffusion tensor imaging of mild to moderate blast-related traumatic brain injury and its sequelae. *J. Neurotrauma* 27, 683–694.
31. Messé, A., Caplain, S., Péligrini-Issac, M., Blanco, S., Montreuil, M., Lévy, R., Lehericy, S., and Benali, H. (2012). Structural integrity and postconcussion syndrome in mild traumatic brain injury patients. *Brain Imaging Behav.* 6, 283–292.
32. Bennett, I.J., Motes, M.A., Rao, N.K., and Rypma, B. (2012). White matter tract integrity predicts visual search performance in young and older adults. *Neurobiol. Aging* 33, 433.e21–433.e31.
33. Goldman-Rakic, P., Selemon, L., and Schwartz, M. (1984). Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. *Neuroscience* 12, 719–743.
34. Jones, D., Christiansen, K., Chapman, R., and Aggleton, J. (2013). Distinct subdivisions of the cingulum bundle revealed by diffusion MRI fibre tracking: implications for neuropsychological investigations. *Neuropsychologia* 51, 67–78.
35. Schmahmann, J.D. and Pandya, D. (2009). Fiber pathways of the brain. OUP USA.
36. Browning, P.G. and Gaffan, D. (2008). Prefrontal cortex function in the representation of temporally complex events. *J. Neurosci.* 28, 3934–3940.
37. Thomas, C., Avram, A., Pierpaoli, C., and Baker, C. (2015). Diffusion MRI properties of the human uncinate fasciculus correlate with the ability to learn visual associations. *Cortex* 72, 65–78.
38. Guskiewicz, K.M., McCrea, M., Marshall, S.W., Cantu, R.C., Randolph, C., Barr, W., Onate, J.A., and Kelly, J.P. (2003). Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *JAMA* 290, 2549–2555.
39. Hiploylee, C., Dufort, P.A., Davis, H.S., Wennberg, R.A., Tartaglia, M.C., Mikulis, D., Hazrati, L.N., and Tator, C.H. (2016). Longitudinal study of postconcussion syndrome: not everyone recovers. *J. Neurotrauma* 34, 1511–1523.
40. American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. American Psychiatric Association: Washington, D.C.
41. Hiploylee, C., Dufort, P.A., Davis, H.S., Wennberg, R.A., Tartaglia, M.C., Mikulis, D., Hazrati, L.N., and Tator, C.H. (2017). Longitudinal study of postconcussion syndrome: not everyone recovers. *J. Neurotrauma* 34, 1511–1523.
42. Shehata, N., Wiley, J., Richea, S., Benson, B.W., Duits, L., and Meeuwisse, W. (2009). Sport Concussion Assessment Tool: baseline values for varsity collision sport athletes. *Br. J. Sports Med.* 43, 730–734.
43. Echemendia, R.J., Meeuwisse, W., McCrory, P., Davis, G.A., Putukian, M., Leddy, J., Makdissi, M., Sullivan, S.J., Broglio, S.P., Raftery, M., Schneider, K., Kissick, J., McCrea, M., Dvořák, J., Sills, A.K., Aubry, M., Engebretsen, L., Loosemore, M., Fuller, G., Kutcher, J., Ellenbogen, R., Guskiewicz, K., Patricios, J., and Herring, S. (2017). The Sport Concussion Assessment Tool 5th Edition (SCAT5): background and rationale. *Br. J. Sports Med.* 51, 848–850.
44. Putukian, M., Echemendia, R., Dettwiler-Danspeckgruber, A., Duliba, T., Bruce, J., Furtado, J.L., and Murugavel, M. (2015). Prospective clinical assessment using Sideline Concussion Assessment Tool-2 testing in the evaluation of sport-related concussion in college athletes. *Clin. J. Sport Med.* 25, 36–42.
45. Yengo-Kahn, A.M., Hale, A.T., Zalneraitis, B.H., Zuckerman, S.L., Sills, A.K., and Solomon, G.S. (2016). The sport concussion assessment tool: a systematic review. *Neurosurg. Focus* 40, E6.
46. Lehman, E.J., Hein, M.J., Baron, S.L., and Gersic, C.M. (2012). Neurodegenerative causes of death among retired National Football League players. *Neurology* 79, 1970–1974.
47. Gardner, R.C. and Yaffe, K. (2015). Epidemiology of mild traumatic brain injury and neurodegenerative disease. *Mol. Cell. Neurosci.* 66, 75–80.
48. Korte, K.B., Horner, M.D., and Windham, W.K. (2002). The trail making test, part B: cognitive flexibility or ability to maintain set? *Appl. Neuropsychol.* 9, 106–109.
49. Lezak, M.D. (2004). *Neuropsychological Assessment*. Oxford University Press: Oxford, U.K.
50. Larrabee, G.J. and Kane, R.L. (1986). Reversed digit repetition involves visual and verbal processes. *Int. J. Neurosci.* 30, 11–15.
51. Peña-Casanova, J., Quiñones-Úbeda, S., Quintana-Aparicio, M., Aguilar, M., Badenes, D., Molinuevo, J.L., Torner, L., Robles, A., Barquero, M.S., and Villanueva, C. (2009). Spanish Multicenter Normative Studies (NEURONORMA Project): norms for verbal span, visuospatial span, letter and number sequencing, trail making test, and symbol digit modalities test. *Arch. Clin. Neuropsychol.* 24, 321–341.
52. Collins, M.W., Grindel, S.H., Lovell, M.R., Dede, D.E., Moser, D.J., Phalin, B.R., Nogle, S., Wasik, M., Cordry, D., and Daugherty, M.K. (1999). Relationship between concussion and neuropsychological performance in college football players. *JAMA* 282, 964–970.
53. Chung, J. (2014). A novel test of implicit memory: an eye tracking study. *Int. J. Appl. Math. Electron. Comput.* 2, 45–48.
54. Pinhas, L., Fok, K.H., Chen, A., Lam, E., Schachter, R., Eizenman, O., Grupp, L., and Eizenman, M. (2014). Attentional biases to body shape images in adolescents with anorexia nervosa: An exploratory eye-tracking study. *Psychiatry Res.* 220, 519–526.
55. Guestrin, E.D., and Eizenman, M. (2006). General theory of remote gaze estimation using the pupil center and corneal reflections. *IEEE Trans. Biomed. Eng.* 53, 1124–1133.
56. Sturm, V., Cassel, D., and Eizenman, M. (2011). Objective estimation of visual acuity with preferential looking. *Invest. Ophthalmol. Vis. Sci.* 52, 708–713.
57. Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., and Flitney, D.E. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 23, S208–S219.
58. Jenkinson, M., Beckmann, C.F., Behrens, T.E., Woolrich, M.W., and Smith, S.M. (2012). Fsl. *Neuroimage* 62, 782–790.

59. Smith, S.M. (2002). Fast robust automated brain extraction. *Hum. Brain Mapp.* 17, 143–155.
60. Galantucci, S., Tartaglia, M.C., Wilson, S.M., Henry, M.L., Filippi, M., Agosta, F., Dronkers, N.F., Henry, R.G., Ogar, J.M., and Miller, B.L. (2011). White matter damage in primary progressive aphasia: a diffusion tensor tractography study. *Brain* 134(Pt 10), 3011–3029.
61. Glasser, M.F. and Rilling, J.K. (2008). DTI tractography of the human brain's language pathways. *Cereb. Cortex* 18, 2471–2482.
62. Hofer, S. and Frahm, J. (2006). Topography of the human corpus callosum revisited—comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *Neuroimage* 32, 989–994.
63. Behrens, T.E., Berg, H.J., Jbabdi, S., Rushworth, M., and Woolrich, M. (2007). Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? *Neuroimage* 34, 144–155.
64. Domesick, V.B. (1970). The fasciculus cinguli in the rat. *Brain Res.* 20, 19–32.
65. Hayes, A.F. (2013). *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*. Guilford Press: New York.
66. Hayes, A.F. (2009). Beyond Baron and Kenny: statistical mediation analysis in the new millennium. *Commun. Monogr.* 76, 408–420.
67. Preacher, K.J. and Kelley, K. (2011). Effect size measures for mediation models: quantitative strategies for communicating indirect effects. *Psychol. Methods* 16, 93.
68. Taghdiri, F., Varriano, B., and Tartaglia, M.C. (2017). Assessment of oculomotor function in patients with postconcussion syndrome: a systematic review. *J. Head Trauma Rehabil.* 32, E55–E67.
69. Williams, I.M., Ponsford, J.L., Gibson, K.L., Mulhall, L.E., Curran, C.A., and Abel, L.A. (1997). Cerebral control of saccades and neuropsychological test results after head injury. *J. Clin. Neurosci.* 4, 186–196.
70. Abel, L., Walterfang, M., Fietz, M., Bowman, E., and Velakoulis, D. (2009). Saccades in adult Niemann-Pick disease type C reflect frontal, brainstem, and biochemical deficits. *Neurology* 72, 1083–1086.
71. Phillipou, A., Douglas, J., Krieser, D., Ayton, L., and Abel, L. (2014). Changes in saccadic eye movement and memory function after mild closed head injury in children. *Dev. Med. Child Neurol.* 56, 337–345.
72. Ettenhofer, M.L., and Barry, D.M. (2016). Saccadic impairment associated with remote history of mild traumatic brain injury. *J. Neuropsychiatry Clin. Neurosci.* 28, 223–231.
73. Camilleri, J.A., Reid, A.T., Müller, V.I., Grefkes, C., Amunts, K., and Eickhoff, S.B. (2015). Multi-modal imaging of neural correlates of motor speed performance in the trail making test. *Front. Neurol.* 6.
74. Pierrot-Deseilligny, C., Rivaud, S., Gaymard, B., and Agid, Y. (1991). Cortical control of memory-guided saccades in man. *Exp. Brain Res.* 83, 607–617.
75. Pierrot-Deseilligny, C., Rivaud, S., Gaymard, B., Müri, R., and Vermersch, A. (1995). Cortical control of saccades. *Ann. Neurol.* 37, 557–567.
76. Müri, R.M., Gaymard, B., Rivaud, S., Vermersch, A.I., Hess, C.W., and Pierrot-Deseilligny, C. (2000). Hemispheric asymmetry in cortical control of memory-guided saccades. A transcranial magnetic stimulation study. *Neuropsychologia* 38, 1105–1111.
77. Pierrot-Deseilligny, C., Müri, R., Ploner, C., Gaymard, B., and Rivaud-Pechoux, S. (2003). Cortical control of ocular saccades in humans: a model for motricity. *Prog. Brain Res.* 142, 3–17.
78. Bussey, T.J., Wise, S.P., and Murray, E.A. (2002). Interaction of ventral and orbital prefrontal cortex with inferotemporal cortex in conditional visuomotor learning. *Behav. Neurosci.* 116, 703.
79. Gong, G., Jiang, T., Zhu, C., Zang, Y., Wang, F., Xie, S., Xiao, J., and Guo, X. (2005). Asymmetry analysis of cingulum based on scale-invariant parameterization by diffusion tensor imaging. *Hum. Brain Mapp.* 24, 92–98.
80. Yan, H., Zuo, X.-N., Wang, D., Wang, J., Zhu, C., Milham, M.P., Zhang, D., and Zang, Y. (2009). Hemispheric asymmetry in cognitive division of anterior cingulate cortex: a resting-state functional connectivity study. *Neuroimage* 47, 1579–1589.
81. Khong, E., Odenwald, N., Hashim, E., and Cusimano, M.D. (2016). Diffusion tensor imaging findings in post-concussion syndrome patients after mild traumatic brain injury: a systematic review. *Front. Neurol.* 7.
82. Song, S.K., Sun, S.W., Ju, W.K., Lin, S.J., Cross, A.H., and Neufeld, A.H. (2003). Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage* 20, 1714–1722.
83. Newcombe, V., Williams, G., Nortje, J., Bradley, P., Harding, S., Smielewski, P., Coles, J., Maiya, B., Gillard, J., and Hutchinson, P. (2007). Analysis of acute traumatic axonal injury using diffusion tensor imaging. *Br. J. Neurosurg.* 21, 340–348.
84. Wilde, E., McCauley, S., Hunter, J., Bigler, E., Chu, Z., Wang, Z., Hanten, G., Troyanskaya, M., Yallampalli, R. and Li, X. (2008). Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. *Neurology* 70, 948–955.
85. Bhatia, K.D., Henderson, L., Ramsey-Stewart, G., and May, J. (2012). Diffusion tensor imaging to aid subgenual cingulum target selection for deep brain stimulation in depression. *Stereotact. Funct. Neurosurg.* 90, 225–232.
86. Keedwell, P.A., Doidge, A.N., Meyer, M., Lawrence, N., Lawrence, A.D., and Jones, D.K. (2016). Subgenual cingulum microstructure supports control of emotional conflict. *Cereb. Cortex* 26, 850–862.
87. Schermuly, I., Fellgiebel, A., Wagner, S., Yakushev, I., Stoeter, P., Schmitt, R., Knickenberg, R., Bleichner, F., and Beutel, M. (2010). Association between cingulum bundle structure and cognitive performance: an observational study in major depression. *Eur. Psychiatry* 25, 355–360.
88. Niogi, S., Mukherjee, P., Ghajar, J., Johnson, C., Kolster, R., Sarkar, R., Lee, H., Meeker, M., Zimmerman, R., and Manley, G. (2008). Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: a 3T diffusion tensor imaging study of mild traumatic brain injury. *Am. J. Neuroradiol.* 29, 967–973.
89. Maruta, J., Suh, M., Niogi, S.N., Mukherjee, P., and Ghajar, J. (2010). Visual tracking synchronization as a metric for concussion screening. *J. Head Trauma Rehabil.* 25, 293–305.
90. Smits, M., Houston, G.C., Dippel, D.W., Wielopolski, P.A., Vernooij, M.W., Koudstaal, P.J., Hunink, M.M., and van der Lugt, A. (2011). Microstructural brain injury in post-concussion syndrome after minor head injury. *Neuroradiology* 53, 553–563.
91. D'souza, M.M., Trivedi, R., Singh, K., Grover, H., Choudhury, A., Kaur, P., Kumar, P., and Tripathi, R.P. (2015). Traumatic brain injury and the post-concussion syndrome: a diffusion tensor tractography study. *Indian J. Radiol. Imaging* 25, 404.
92. Maruta, J., Palacios, E.M., Zimmerman, R.D., Ghajar, J., and Mukherjee, P. (2016). Chronic post-concussion neurocognitive deficits. I. Relationship with white matter integrity. *Front. Hum. Neurosci.* 10.
93. Cubon, V.A., Putukian, M., Boyer, C., and Dettwiler, A. (2011). A diffusion tensor imaging study on the white matter skeleton in individuals with sports-related concussion. *J. Neurotrauma* 28, 189–201.
94. Dyrby, T.B., Søgaard, L.V., Parker, G.J., Alexander, D.C., Lind, N.M., Baaré, W.F., Hay-Schmidt, A., Eriksen, N., Pakkenberg, B., and Paulson, O.B. (2007). Validation of in vitro probabilistic tractography. *Neuroimage* 37, 1267–1277.
95. Descoteaux, M., Deriche, R., Knosche, T.R., and Anwander, A. (2009). Deterministic and probabilistic tractography based on complex fibre orientation distributions. *IEEE Trans. Med. Imaging* 28, 269–286.

Address correspondence to:

Maria Carmela Tartaglia, MD, FRCPC
Tanz Centre for Research in Neurodegenerative Diseases
University of Toronto
60 Leonard Avenue
Toronto, Ontario M5T 2S8
Canada

E-mail: foad.taghdiri@mail.utoronto.ca