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Research paper

Altered motor system function in post-concussion syndrome as assessed via transcranial magnetic stimulation

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ABSTRACT

Objective: It is unclear why specific individuals incur chronic symptoms following a concussion. This exploratory research aims to identify and characterize any neurophysiological differences that may exist in motor cortex function in post-concussion syndrome (PCS).
Methods: Fifteen adults with PCS and 13 healthy, non-injured adults were tested. All participants completed symptom questionnaires, and transcranial magnetic stimulation (TMS) was used to measure intracortical and transcallosal excitability and inhibition in the dominant motor cortex.
Results: Cortical silent period ($p = 0.02$, $g = 0.96$) and ipsilateral silent period ($p = 0.04$, $g = 0.78$) were shorter in the PCS group compared to the control group which may reflect reduced GABA-mediated inhibition in PCS. Furthermore, increased corticomotor excitability was observed in the left hemisphere but not the right hemisphere.
Conclusions: These data suggest that persistent neurophysiological differences are present in those with PCS. The exact contributing factors to such changes remain to be investigated by future studies.
Significance: This study provides novel evidence of lasting neurophysiological changes in PCS.

1. Introduction

Concussion, also known as mild traumatic brain injury (mTBI), is globally one of the most prevalent injuries as it affects more than 40 million individuals each year (Gardner and Yaffe, 2015). While most recover within the first 10 days following injury, symptoms persist in 10–50% of individuals for months or years following injury (Hou et al., 2012; Sigurdardottir et al., 2009; Sterr et al., 2006; Theadom et al., 2016). When symptoms persist beyond 3 months, the diagnosis is termed post-concussion syndrome (PCS).

At this time, the underlying cause of PCS remains unclear. Pre-injury factors may help predict PCS development in humans. For example, PCS is more common in females, in those whom have had multiple concussions, or those with psychological diagnoses (Tator et al., 2016). Factors directly related to the injury do not appear to provide additional predictive value. Loss of consciousness at the time of injury does not correlate with PCS occurrence (Sterr et al., 2006), and a comparison of mild and severe injury groups revealed similar PCS prevalence 1 year post-injury (Sigurdardottir et al., 2009). It is important to note that injuries of any severity may result in chronic symptoms, further necessitating an objective measure to identify individuals who remain chronically affected post-injury.

At present there are no objective biological markers to identify and track recovery changes in individuals with PCS. Plasma-based markers such as tau protein have shown some potential (Zetterberg and Blennow 2015), however peripheral blood measures do not necessarily reflect central nervous system metabolite concentrations. Neuroinflammation has also been hypothesized to contribute to PCS development, although human evidence is still forthcoming (Rathbone et al., 2015). An alternative is to examine neurological function specifically in those who develop PCS.

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Table 1
TMS findings in concussion.

Measure	Asymptomatic (>3 months)	PCS > 3 months)
RMT	Ø (De Beaumont et al., 2007; Pearce et al., 2014, 2018; Davidson and Tremblay, 2016) ↑ (Tallus et al. 2012)	↑ (Tallus et al., 2012)
SICI	Ø (De Beaumont et al., 2007, 2009, b; Tremblay et al., 2014; Pearce et al., 2018)	↑ (Pearce et al., 2019)
ICF	Ø (De Beaumont et al. 2007, 2009)	~
CSP	↑ (De Beaumont et al., 2007, 2009, 2011, 2012b; Tremblay et al., 2011) Ø (Davidson and Tremblay, 2016; Tremblay et al., 2014) ↓ (Pearce et al., 2014, 2018)	↑ (Pearce et al., 2019)
iSP	↓ (Davidson and Tremblay, 2016)	~
IHI	~	~

↑ = increase, ↓ = decrease, Ø = no change with history of injury. ~indicates unknown. CSP: cortical silent period; ICF: intracortical facilitation; IHI: interhemispheric inhibition; iSP: ipsilateral silent period; PCS: post-concussion syndrome; RMT: resting motor threshold; SICI: short-interval intracortical inhibition;

The aforementioned neurometabolic cascade that occurs post-injury is known to impact neurotransmission (Guerriero et al., 2015), and this has implications for neural function which can be assessed using transcranial magnetic stimulation (TMS). TMS is a non-invasive brain stimulation tool, commonly used to measure corticospinal and cortical excitability in the primary motor cortex (M1). Though TMS has already been used to study cortical and corticomotor excitability in the long-term following concussion, these studies have tended to investigate asymptomatic individuals. Nevertheless, changes in cortical neurophysiology within M1 are noted in recovered cohorts. Most commonly, TMS has been used to induce a cortical silent period (CSP), whereby M1 stimulation briefly interrupts voluntary tonic contraction in a muscle of the limb contralateral to the site of stimulation (Wilson et al., 1993). Asymptomatic groups with a history of concussion have a longer CSP than non-injured controls, and this pattern has been observed up to 30 years post-injury (De Beaumont et al., 2007, 2009, 2011, 2012a,b, Tremblay et al., 2011).

It is less clear how TMS measures such as CSP differ in those with PCS (Table 1). A recent study found that adults with PCS show greater intracortical inhibition compared to asymptomatic adults with a history of concussion and healthy controls (Pearce et al., 2019). This was observed through increases in 3 different TMS measures including the aforementioned CSP, short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI). All 3 measures are thought to reflect intracortical GABAergic inhibition (Ziemann et al., 2015). It is currently unknown whether other TMS measures such as intracortical facilitation (ICF), reflective of NMDA receptor activity, or measures of transcallosal inhibition between motor cortices are impacted in PCS.

The goal of this study was to measure and compare M1 neurophysiology between PCS and healthy control subjects. TMS was used to assess corticospinal excitability, intracortical facilitation and inhibition, and transcallosal inhibition between motor cortices. If differences between groups exist, this could be suggestive of a novel neurological biomarker of PCS.

2. Materials and methods

2.1. Participants

Fifteen individuals with PCS (mean age 28.8 ± 8.7 years, 11 female) and 13 healthy controls without history of concussion (mean age 26.8 ± 7.7 years, 10 female) participated (Table 2). Individuals with PCS were recruited from a Hamilton clinic database, McMaster University, and the Hamilton community. Control group participants were also recruited from McMaster University and the Hamilton community. To ensure a chronically symptomatic sample was acquired, concussion participants must have remained symptomatic for a minimum of 6 months following a medically

Table 2
Participant demographics.

I) Individual PCS participants

Participant	Age	Sex	Months Since Last	PCSS	BDI-II	# of concussions
1	37	M	9	12	3	5
2	24	M	23	65	23	4
3	24	F	8	20	10	1
4	21	M	20	69	23	6
5	19	F	18	108	8	4
6	43	F	8	81	11	1
7	19	F	59	72	17	1
8	32	F	26	63	17	1
9	41	F	12	28	10	3
10	21	M	30	35	10	1
11	44	F	20	78	17	1
12	24	F	15	91	19	3
13	25	F	30	45	7	3
14	29	F	16	53	24	1
15	29	F	22	79	8	1

II) Individual control participants

Participant	Age	Sex	PCSS	BDI-II
1	23	F	4	9
2	22	M	17	9
3	23	M	3	0
4	20	F	4	2
5	21	F	10	1
6	32	F	3	0
7	21	M	3	6
8	22	F	2	2
9	23	F	19	7
10	30	F	45	2
11	39	F	7	1
12	45	F	29	4
13	27	F	0	0

III) Group-averaged demographics

	PCS	CON	p (Hedge's *g*)
n	15 (11 female)	13 (10 female)	
Age[$]	28.80 ± 8.69	26.77 ± 7.75	0.52 (0.25)
PCSS[**,$]	59.9 ± 27.4	11.2 ± 13.2	**<0.01 (2.22)**
BDI-II[**,$]	13.8 ± 6.6	3.3 ± 3.4	**<0.01 (1.96)**
Time since last	21.1 ± 12.7	N/A	
# of concussions (self-reported)	1: n = 8 2+: n = 7	N/A	

[**] $p < 0.01$.
[$] Indicates a Mann-Whitney U *t*-test was performed.

diagnosed concussion without further head injury in the interim. Symptom persistence was confirmed on the day of testing in all concussion participants based on a post-concussion symptom scale (PCSS) score equal to or greater than 12 (mean = 59.9 ± 27.4, median = 65) (Lovell et al., 2006). A cut-off score of 12 was determined *a priori* based on existing literature (Lovell et al., 2006). Participants completed the Beck's Depression Inventory (BDI-II) to identify the presence of depression, a common symptom associated with concussion. To minimize the confounding effects of comorbid depression, individuals who scored greater than 29 were excluded (i.e. severe depression was excluded), along with those with previous or current psychiatric diagnoses (Beck et al., 1988). Participants were excluded if taking medications with known interactions with GABA or NMDA receptors including; psychiatric medications, any other depressants or stimulants, and medications that may reduce the threshold for seizure. All participants were confirmed right-hand dominant using a modified handedness questionnaire (Oldfield, 1971), were screened for contraindications to TMS, and provided informed written consent prior to participation. This study was approved by the Hamilton Integrated Research Ethics Board and conformed to the standards of the *Declaration of Helsinki*.

2.2. Electromyography

EMG recordings were acquired from the first dorsal interosseous (FDI) muscle of both right and left hands using 9 mm Ag-AgCl surface electrodes. A wet ground was secured around the right forearm, distal to the elbow. All EMG recordings were amplified 1000× (Model 2024F; Intronix Technologies Corporation, Bolton, Ontario, Canada) and were band-pass filtered between 20 Hz and 2.5 kHz. Data was digitized using an analog-to-digital interface at 5 kHz (Power 1401; Cambridge Electronics Design, Cambridge, UK) and subsequently analysed using Signal software (Signal, version 6.02; Cambridge Electronics Design).

2.3. Maximum voluntary contraction

MVC was acquired from the right FDI only. Participants were asked to maximally contract the right FDI against an immovable, fixed beam. Three trials of 5 s were performed with ~1 min of rest in between trials. Signals were rectified and displayed on an oscilloscope (Tektronix TDS2004c, USA) to provide participants with visual feedback.

2.4. Transcranial magnetic stimulation

Two custom figure-of-eight coils (50 mm diameter) connected to two Magstim 200^2 stimulators (Magstim, Whitland, UK) were used for TMS delivery. A Bistim module was attached to one of the two stimulators which were connected in parallel for paired-pulse stimulation paradigms. One coil was always used to deliver TMS over left M1, and the second coil was used over right M1. Coils were positioned at a 45° angle from the sagittal plane to induce a posterior-to-anterior current within the cortex. To ensure consistent TMS delivery, coil location and orientation were digitally registered on a standard magnetic resonance imaging (MRI) image using Brainsight neuronavigation (Rogue Research, Montreal, Quebec City, Canada). TMS coils were held over each right and left 'motor hotspot', defined as the cortical locations that optimally elicit large and consistent motor-evoked potentials (MEPs) in the contralateral FDI for each hemisphere. These locations were used for all TMS measures. Resting motor threshold (RMT) was obtained at the motor hotspot for each hemisphere as a metric for corticospinal excitability. RMT was measured using ML-PEST software (TMS Motor Threshold Assessment Tool; MTAT, version 2.0) which uses a predictive algorithm to accurately determine RMT after 20 stimuli (Ah Sen et al., 2017). The initial settings were set to *a priori* and the initial stimulus intensity was set to 37% of the maximum stimulator output. Active motor threshold (AMT) was acquired for the right FDI only while the muscle was contracted to 10% of the participant's MVC using the same methodology as RMT (Ah Sen et al., 2017). The stimulus intensity to evoke a MEP of 1 mV was determined for each hemisphere. This was determined by delivering 15 TMS pulses at an intensity expected to evoke a mean MEP amplitude between 0.8 and 1.2 mV. If the mean MEP amplitude was above or below these thresholds, the stimulator intensity was adjusted accordingly and the procedure was repeated.

2.5. Paired-pulse TMS

Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were recorded from the right FDI with the conditioning stimulus (CS) intensity set to 90% AMT and the test stimulus (TS) set to evoke a MEP of 1 mV in peak-peak amplitude. The interstimulus interval (ISI) was set at 2 ms and 15 ms for SICI and ICF, respectively. Fifteen TS alone trials were randomized among 30 CS-TS trials (15 for SICI and 15 for ICF), with an inter-trial interval of 5 s.

2.6. Silent periods

To measure cortical silent period (CSP) from the right FDI, participants maintained tonic muscle activation of the right FDI at 10% MVC for 5 s per trial. TMS was delivered to left M1 at the intensity that evoked a 1 mV MEP in right FDI at rest for 15 trials.

To measure ipsilateral silent period (iSP), TMS was delivered to the right M1 at the intensity that evoked a 1 mV MEP in the left FDI muscle while participants maintained a tonic muscle contraction of 50% MVC in the right FDI (Kuo et al., 2017). Fifteen trials were acquired, separated into three collections of 5 trials, each separated by ~1 min to reduce the influence of muscle fatigue.

2.7. Interhemispheric inhibition

A conditioning TMS pulse was delivered to the right hemisphere (CS), preceding TMS delivered to the left hemisphere (TS) by 10 ms or 40 ms to acquire short-interval interhemispheric inhibition (SIHI) and long-interval interhemispheric (LIHI), respectively, in the right FDI. The intensity of the CS and TS were set to evoke a MEP of ~1 mV peak-to-peak amplitude in the left and right FDI muscle, respectively. Fifteen TS alone trials were randomized among 30 CS-TS trials (15 for SIHI, 15 for LIHI), with an inter-trial interval of 5 s.

2.8. Data reduction and analysis

Each trial was analysed for excessive EMG using an 8 ms window immediately prior to the first TMS artefact. Any trial with peak-to-peak muscle activity greater than 50 μV within that window was excluded from analysis with the exception of CSP and iSP where voluntary activation was a requirement (Turco et al., 2018). Accordingly, a small number of trials were omitted from analysis for SICI (1.3%), ICF (1.4%), SIHI (1.1%), and LIHI (0.6%). Any individual data set in which >25% of trials had contaminated EMG activity was omitted from analysis. This occurred on three occasions, resulting in the removal of one dataset from each of short-interval intracortical inhibition, cortical silent period, and ipsilateral silent period analysis. For two participants, multiple measures had systematic background noise present at a frequency of ~60 Hz. To account for this, an additional notch filter was applied with a center at 60 Hz and a width of 8 Hz.

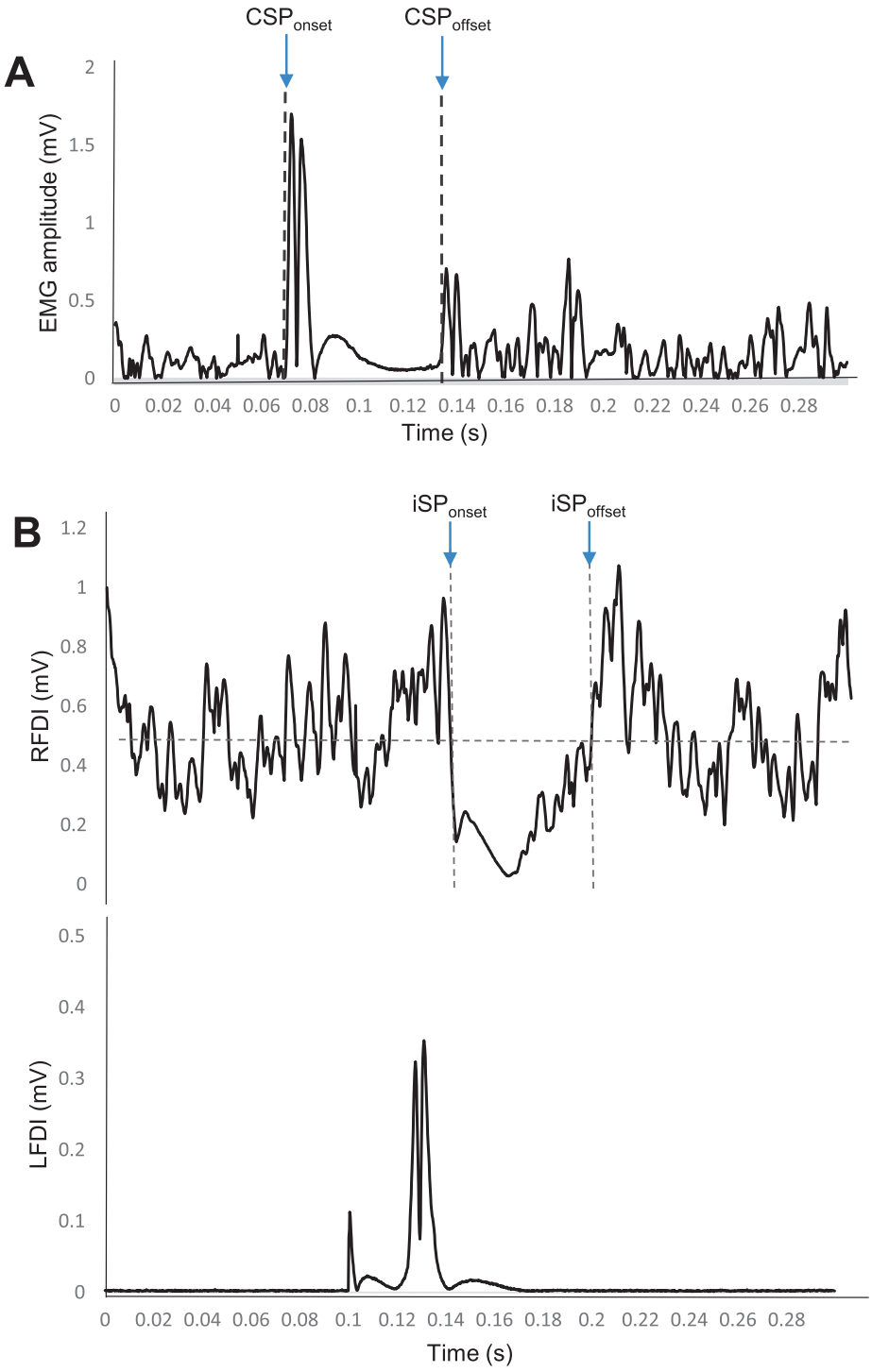

Fig. 1. (A) Exemplar CSP analysis. CSP length was quantified using the described technique (see methods); CSP length = CSP offset – CSP onset. (B) Eemplar iSP analysis. ISP was quantified using the described technique (see methods), where interrupted voluntary EMG activity in the right FDI can be seen in the top row and the MEP evoked in the left FDI can be seen on the bottom. iSP length = iSP offset – iSP onset; LTI = iSP onset – TMS onset.

Fig. 1 displays an example analysis for CSP (1A) and iSP (1B). CSP duration was measured in each of 15 trials and subsequently averaged for each participant. CSP was independently analysed by two blinded raters and the two scores were averaged. Analysis was performed using a semi-automated approach adapted from previous work (Kimberley et al., 2009; Murase et al., 2005). EMG recordings were first rectified, and the mean EMG amplitude was determined from a 25 ms window immediately preceding the TMS pulse. CSP onset was defined as the beginning of the TMS-evoked response. CSP offset was defined as the beginning of the first consecutive 2 ms period of EMG activity exceeding the mean following the silent period. Although previous research using this method determined CSP offset based on 50% of the mean EMG activity, this was altered to accommodate the lower tonic muscle activation in this study (Kimberley et al., 2009; Murase et al., 2005). Once CSP onset and offset were determined, CSP length was calculated as the difference between them. Of the 28 participants, 26 datasets were analysed. One dataset was removed due

to excessive muscle activity in the left FDI, and the other was removed because excessive electrostatic noise interfered with accurate CSP determination. For data included in CSP analysis, 24 of 390 (6.2%) trials were removed due to excessive muscle activation of the left FDI or the absence of an observable CSP.

Fifteen trials were gathered for each participant to determine iSP. Trials were rectified, then averaged and the mean EMG amplitude was measured during a 90 ms pre-stimulus window immediately preceding the TMS pulse. A horizontal cursor was placed at the pre-stimulus mean amplitude and iSP onset was determined as the first consecutive 5 ms period with EMG activity below the mean following MEP onset in the left FDI (Davidson and Tremblay 2016). ISP offset was defined as the initiation of the first consecutive 2 ms period of EMG activity above the mean following iSP onset. These data points were used to determine iSP length (iSP = iSP offset – iSP onset) and the onset latency of transcallosal inhibition (LTI = iSP onset – TMS onset). If EMG activity did not fall below the mean for a consecutive 5 ms period, following MEP onset, then it was determined that the iSP could not be adequately identified in that individual's data set. This was the case for 3 of the 28 data sets. One other data set was omitted due to electromagnetic noise interference, and a fifth data set was removed due to EMG contamination in left hand recording

3. Statistical analyses

All measures were assessed for normality using Shapiro-Wilk tests. Extreme outliers identified using SPSS software (IBM), defined as 3 times the interquartile range, were removed. First, a Conover's ANOVA was performed on all paired-pulse TMS measures to determine whether CS pulses significantly influenced the TS-evoked MEPs (i.e. to determine if inhibition/facilitation is significantly present) (Conover and Iman, 1982). For SICI and ICF, a two-way Conover's ANOVA, with between-subject factor GROUP (two levels: PCS, CONTROL) and within-subject factor PATTERN (two levels: TS, CS-TS) was performed. For SIHI and LIHI, a two-way Conover's ANOVA with between-subject factor GROUP (two levels: PCS, CONTROL) and within-subject factor PATTERN (3 levels: TS, CS, CS-TS) was performed. Next, between-group differences of normally distributed data were analysed using Welch's *t*-test, and non-normal data was analysed using a Mann-Whitney *U* test. A two-way mixed model intraclass correlation was performed to assess inter-rater reliability for CSP analysis. All data is presented as means ± standard deviation, and statistical significance was considered as $p < 0.05$. Effect sizes were calculated using Hedge's *g*.

4. Results

4.1. Participant demographics

Table 2 shows demographics from all participants. All participants successfully completed the experiment with no adverse events. The PCS group scored significantly higher on the PCSS ($p < 0.01$) and BDI-II questionnaires ($p < 0.01$).

4.2. Corticomotor excitability

No significant differences were observed between groups for any measure of corticomotor excitability (see Table 3), with the exception of RMT in right FDI whereby thresholds were lower in the PCS group ($p = 0.03$).

4.3. Cortical excitability

In ICF, a main effect of PATTERN ($F_{(1,25)} = 19.43$; $p < 0.01$) was observed, confirming that the expected facilitation was present in both groups. The amount of facilitation observed did not differ between groups ($p = 0.73$).

4.4. Cortical inhibition

In SICI, a main effect of PATTERN ($F_{(1,25)} = 61.44$; $p < 0.01$) was observed, indicating that inhibition was seen in both groups (see Table 4). The magnitude of SICI was not different between groups ($p = 0.60$).

Table 3
TMS between-group data.

Measure (group = n)	PCS Mean ± SD	CON Mean ± SD	p-value (Hedge's *g*)
Corticomotor Excitability			
RMT-RFDI* (PCS = 15, CON = 13)	38.47 ± 5.25	44.46 ± 8.72	**0.03 (0.85)**
RMT-LFDI (PCS = 15, CON = 13)	40.93 ± 8.28	42.77 ± 7.97	0.56 (0.23)
AMT-RFDI (PCS = 15, CON = 13)	29.47 ± 3.93	31.46 ± 3.78	0.18 (0.52)
1 mV-RFDI (PCS = 15, CON = 13)	49.27 ± 11.19	55.54 ± 12.04	0.18 (0.54)[$]
1-mV-LFDI (PCS = 15, CON = 13)	50.27 ± 12.50	54.92 ± 15.31	0.61 (0.34)[$]
Cortical Excitability			
ICF (PCS = 15, CON = 12)[#]	1.30 ± 0.32	1.21 ± 0.31	0.73 (0.30)[$]
Cortical Inhibition			
SICI (PCS = 14, CON = 13)[#]	0.49 ± 0.27	0.55 ± 0.32	0.60 (0.21)
CSP* (PCS = 13, CON = 13)[#]	112 ± 31 ms	141 ± 29 ms	**0.02 (0.96)**
Transcallosal Inhibition			
SIHI (PCS = 15, CON = 13)	0.58 ± 0.24	0.64 ± 0.41	0.64 (0.18)
LIHI (PCS = 15, CON = 13)	0.69 ± 0.22	0.70 ± 0.32	0.92 (0.04)
iSP (PCS = 10, CON = 13)[#]	20.2 ± 13.3 ms	30.6 ± 13.2 ms	**0.04 (0.78)[$]**
LTI (PCS = 10, CON = 13)[#]	35.8 ± 5.0 ms	33.7 ± 3.5 ms	**0.14 (0.50)[$]**

RMT, AMT, and 1 mV results are reported as a percentage of maximum stimulator output (%MSO). Paired-pulse measures were calculated as the ratio of the mean conditioned stimulus divided by the mean unconditioned stimulus (CS-TS/TS) for each participant.
The following data was excluded from analysis: SICI (PCS = 1), EMG contamination; ICF (CON = 1), extreme outlier; CSP (PCS = 2), no observable silent period (1), EMG contamination (1); iSP (PCS = 5), no observable silent period (3), EMG contamination (2). * indicates $p < 0.05$. [#] indicates that some data was omitted from the analysis. [$] indicates a Mann-Whitney U *t*-test was used for statistical analysis, otherwise a Welch's *t*-test was performed.

Table 4
Paired-pulse measures.

Measure (group = n)	TS Mean ± SD	CS Mean ± SD	CS-TS Mean ± SD	Conover's ANOVA
SICI (PCS = 14, CON = 13)[#]	PCS = 1.07 ± 0.23 CON = 1.07 ± 0.23	~	PCS = 0.50 ± 0.26 CON = 0.55 ± 0.27	**PATTERN: $F_{(1,25)}$ = 61.44; p < 0.01**, g = 2.19 PATTERN*GROUP: $F_{(1,25)}$ = 0.06; p = 0.81, g = 0.09 GROUP: $F_{(1,25)}$ = 0.20; p = 0.66, g = 0.10
ICF (PCS = 15, CON = 12)[#]	PCS = 1.06 ± 0.22 CON = 1.07 ± 0.22	~	PCS = 1.38 ± 0.51 CON = 1.28 ± 0.38	**PATTERN: $F_{(1,25)}$ = 19.43; p < 0.01**, g = 0.76 PATTERN*GROUP: $F_{(1,25)}$ = 0.77; p = 0.39, g = 0.34 GROUP: $F_{(1,25)}$ = 0.02; p = 0.90, g = 0.16
SIHI (PCS = 15, CON = 13)	PCS = 1.01 ± 0.26 CON = 1.03 ± 0.27	PCS = 0.96 ± 0.67 CON = 1.02 ± 0.58	PCS = 0.57 ± 0.22 CON = 0.65 ± 0.43	**PATTERN: $F_{(1,26)}$ = 15.53; p < 0.01** CS v TS: p = 0.27, g = 0.06 **TS v CS-TS: p < 0.01, g = 1.36** **CS v CS-TS: p < 0.01, g = 0.75** PATTERN*GROUP: $F_{(1,26)}$ = 0.20; p = 0.82, g = 0.17 GROUP: $F_{(1,26)}$ = 1.14; p = 0.30, g = 0.13
LIHI (PCS = 15, CON = 13)	PCS = 1.01 ± 0.26 CON = 1.03 ± 0.27	PCS = 0.89 ± 0.56 CON = 1.03 ± 0.43	PCS = 0.70 ± 0.31 CON = 0.70 ± 0.33	**PATTERN: $F_{(1,26)}$ = 7.68; p < 0.01** CS v TS: p = 0.39, g = 0.16 **TS v CS-TS: p < 0.01, g = 1.09** CS v CS-TS: p = 0.07 g = 0.61 PATTERN*GROUP: $F_{(1,26)}$ = 0.31; p = 0.65, g = 0.21 GROUP: $F_{(1,26)}$ = 0.94; p = 0.34, g = 0.15

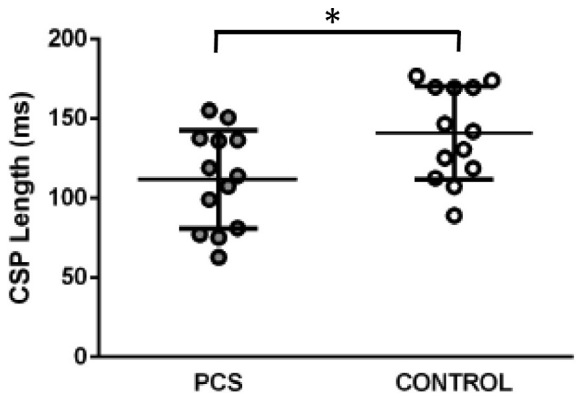

Fig. 2. Cortical Silent Period data with means and standard deviation plotted. For PCS participant 1, CSP could not be accurately quantified using the described criteria (see methods). For PCS participant 11, CSP could not be accurately quantified due to EMG contamination. These 2 individuals were omitted from any CSP analysis. *p < 0.05.

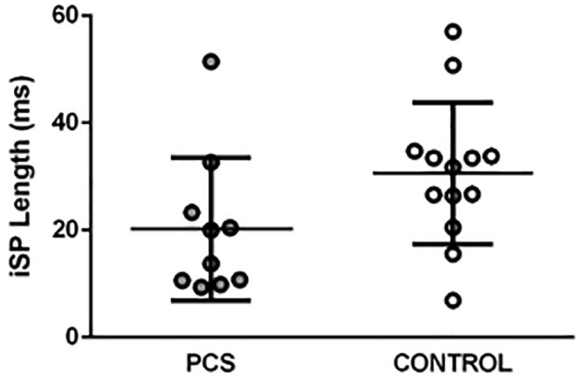

Fig. 3. Ipsilateral Silent Period individual data with means and standard deviations are plotted. PCS participants 3, 6, and 10 did not evoke observable silent periods. PCS participants 4 and 11 could not be accurately quantified due to EMG contamination. These 5 individuals were omitted from iSP and LTI analyses. *p < 0.05.

CSP was significantly reduced in the PCS group (p = 0.02) (Fig. 2). For CSP assessments, inter-rater reliability was excellent (ICC = 0.98, 95% confidence interval) between the two blinded raters. Of note, it has been shown that at increased stimulation intensity, MEP amplitude and CSP increase (Wilson et al., 1993). Importantly, MEP amplitudes evoked during CSP acquisition did not differ between groups (p = 0.20).

4.5. Transcallosal inhibition

SIHI and LIHI were observed in both groups and did not significantly differ between groups. Reduced iSP length was observed in the PCS group (p = 0.04, g = 0.78) (Fig. 3). LTI was similar between groups (p = 0.28). Notably, iSP was not observed in 3 participants from our PCS group, and these data were not included in the analyses. MEP amplitudes were not significantly different between groups and thus are unlikely to have influenced these results (p = 0.14).

5. Discussion

This study provides evidence of neurological differences present in PCS compared to controls. There are three notable findings. First, CSP was reduced in PCS compared to the control group. Second, we observed reduced iSP in the PCS group but no difference in IHI between groups. Third, reduced RMT was measured in the left hemisphere suggesting greater corticospinal excitability in PCS compared to healthy controls.

Reduced CSP length was seen in the PCS group compared to healthy controls. This contrasts with the majority of findings in recovered concussion groups demonstrating increased CSP (De Beaumont et al., 2007, 2009, 2011, 2012a; Tremblay et al., 2011) though others observed no change in CSP (Davidson and Tremblay 2016; Tremblay et al., 2014), or reduced CSP (Pearce et al., 2014, 2018). Of note, the two studies that observed reduced CSP in asymptomatic concussion groups also reported slower reaction time and poorer dexterity in the concussion groups which correlated with reduced CSP (Pearce et al., 2014, 2018). Based on these functional deficits, it is possible that the concussion groups in these two studies remained symptomatic in some aspect of motor control although no measure was acquired regarding the subjective symptom experience of these groups. To date, only two studies have measured CSP in a chronically symptomatic population. A recent study found CSP to be similar in symptomatic, asymptomatic and non-injured youth 4–6 weeks following injury (Seeger et al., 2017). A lack of difference among groups may relate to the immature nervous system influencing corticospinal

excitability, or relate to a unique criteria for defining PCS as 1 month post-injury in that study (Nezua et al., 1997). Most recently in adults, CSP was greater in a PCS group compared with a recovered group and a healthy control group (Pearce et al., 2019). The differential findings related to CSP length between Pearce et al. (2019) and the present study may be due to a multitude of methodological factors ultimately affecting the heterogeneity of the PCS samples tested. This includes the use of antidepressants, symptom severity and the number of acquired concussions. In Pearce et al. (2019), 25% of the PCS participants were using antidepressants in contrast to our study where individuals were excluded if taking antidepressants. Previous work has shown that the chronic use of antidepressants increases $GABA_B$ receptor activity which may increase CSP length (Ghose et al., 2011; Ziemann et al., 2015). Further, symptom severity was not assessed in the same manner between studies. Here, we used the entire PCSS to classify symptom severity while Pearce et al. (2019) used a subset of the PCSS related to fatigue. Therefore, it is unknown whether symptom severity is comparable or different between studies. This may have contributed to the differential findings since symptom severity is related to structural changes in parietal grey matter (Dean et al., 2015) and therefore, may lead to an alteration in motor cortex excitability. In addition, we note that the mean number of previously diagnosed concussions was 4 in Pearce et al. (2019) and 2.4 in the present study. It has recently been reported that rats with multiple mTBI's exhibit greater structural changes than those with a single mTBI (Kulkarni et al., 2019). Further, De Beaumont et al. (2007) has shown that CSP length increases in asymptomatic concussed individuals after they acquire another subsequent concussion.

A possible explanation for a shorter CSP in the PCS group may relate to greater presence of concussion symptoms and/or depressive symptoms. It has been shown that injury severity predicts longer CSP (De Beaumont et al., 2007), however it is not clear how this translates to the influence of symptom severity in the chronic phase of injury. Previous work in former athletes with a concussion history found shorter CSP compared to healthy controls and this was associated with poorer fine motor control (Pearce et al., 2014). It is unclear whether motor control impairment could explain the findings in the present study as we did not directly assess motor control. Reduced CSP has been found in major depressive disorder (MDD) patients compared to controls (Bajbouj et al., 2006; Levinson et al., 2010), and classic anti-depressants such as selective serotonin reuptake inhibitors (SSRI's) are shown to increase CSP length (Robol et al., 2004). Although this study did not explore the relationship between CSP length and symptom severity (PCSS or BDI), future studies with larger sample sizes may be able to address this question.

This study is the first to assess iSP and IHI in a chronically symptomatic concussion population. Although the pharmacology underlying iSP and IHI are not entirely clear, they are thought to operate via excitatory transcallosal projections interacting with local inhibitory GABAergic interneurons (Daskalakis et al., 2002; Ferbert et al., 1992; Perez and Cohen 2008). (Perez and Cohen 2009). IHI was not different between the PCS and control groups, however, between-group comparison of iSP revealed a shorter silent period in the PCS group. Based on the suggested neurophysiology underpinning iSP, differences in this metric may indicate either disrupted excitatory transcallosal neurotransmission or reduced activity of local GABAergic interneurons. Diffusion tensor imaging (DTI) and diffusion-weighted imaging (DWI) have shown microstructural damage to the corpus callosum acutely following injury (D'Souza et al., 2015; Messé et al., 2011; Smits et al., 2011), which is present to a greater degree in those who incur PCS (Messé et al., 2011). Therefore, one explanation for reduced iSP in PCS could be that reduced excitatory transcallosal signal resulted in less activation of local GABAergic interneurons. This explanation is unlikely given that signal latency (LTI) and measures of IHI were unaffected. A more likely explanation is that reduced local inhibitory control of corticospinal projections is responsible for reduced iSP. The latter explanation could align with the present finding of reduced CSP in the PCS group, a measure also thought to reflect GABAergic activity (Ziemann et al., 2015), however it is unknown whether these measures reflect similar neuronal populations. Future studies should continue to assess transcallosal function in PCS using TMS in conjunction with advanced neuroimaging techniques to build upon the present findings.

We observed lower RMT for the right FDI in the PCS group compared to the control group. This evidence of greater corticospinal excitability is in-line with the notion that concussion results in greater excitatory input due to greater glutamate release and binding with post-synaptic NMDA receptors (Guerriero et al., 2015). Further, MRS has shown elevated glutamate concentration in M1 6 months following concussion which may explain the reduction in RMT, a measure that reflects glutamatergic activity of corticospinal neurons (Paulus et al., 2008). Notably, a reduction in RMT was observed only in the left hemisphere (right FDI). This may be explained by previous research demonstrating that the left hemisphere is particularly vulnerable to microstructural damage caused by concussive injury (Cubon et al., 2011; Mayer et al., 2010). Imaging work has demonstrated microstructural changes that are observed only in the left hemisphere in the semi-acute phase of injury (Mayer et al., 2010). Such asymmetries may remain in the months following injury and could explain the hemisphere-specific reduction in RMT observed in our PCS group, though this remains speculative. This finding may also relate to hand dominance as all participants were right-hand dominant. Previous research has shown that dominant hand muscles occupy greater cortical territory than non-dominant hand muscles (Dassonville et al., 1997; Nicolini et al., 2019; Triggs et al., 1999). In contrast to our findings, one study reports increased RMT in adults with PCS (Tallus et al., 2012). Although reduced GABAergic inhibition in our PCS cohort may seem to offer an explanation for this discrepancy, this logic is weakened by evidence indicating that pharmacological manipulation of GABAergic neurotransmission did not affect motor thresholds (Kähkönen and Ilmoniemi 2004). While the present discrepancy is unclear, corticospinal excitability seems to be affected in PCS and warrants further investigation.

In conclusion, the main findings of the present study identify reductions in GABA-mediated TMS measures, both transcallosal and intracortical, in the PCS group compared to controls. This suggests reduced GABAergic control of motor systems in PCS patients. We also observed evidence of hemisphere-specific changes in corticomotor excitability in PCS. Future investigations of PCS should monitor the presence of a variety of concussion symptoms including depression to better elucidate the value of corticospinal and inhibitory cortical measures, in particular CSP, as specific markers of PCS. It would also provide great value for future research to track TMS outcomes from the acute phase into the chronic phase following concussion to confirm whether similar differentiating outcomes emerge between those who recover typically and those who incur PCS.

Authors Disclosure Statement

The authors have no conflicts to disclose.

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