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Neurophysiological abnormalities in individuals with persistent post-concussion symptoms

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Abstract—Concussion injury results in a rapid onset of transient neurological impairment that can resolve quickly, or sometimes evolve over time, but usually resolve within seven to 10 days. However, a small but noticeable cohort (~10%) of individuals continues to experience persistent lingering effects, particularly fatigue, recognized as post-concussion symptoms (PCS). This study explored neurophysiological mechanisms in people with persistent PCS. Studies involved using self-report post-concussion fatigue scale, transcranial magnetic stimulation (TMS) and somatosensory stimulation in those with diagnosed PCS (n = 20; 36.1 ± 14.0 yr., 4 female; mean time post-concussion 15.4 ± 7.6 months) to fully recovered individuals (n = 20; 33.8 ± 6.6 yr., 2 female; post-concussion 12.9 ± 6.6 months) and healthy controls (n = 20; 37.7 ± 8.0 yr., 3 female). PCS participants demonstrated a significantly higher self-report fatigue (score: PCS 20.2 [95% CI 17.4–22.9], Recovered 6.2 [3.1–9.3], Control 2.75 [0.6–4.8]). PCS participants showed a worsening of reaction time ($F_{2,57}$ = 4.214; p = 0.020) and increased reaction time variability ($F_{2,57}$ = 5.505; p = 0.007). Somatosensory differences were observed for amplitude discrimination ($F_{2,57}$ = 5.166; p = 0.009), temporal order judgment ($F_{2,57}$ = 4.606; p = 0.014) and duration discrimination ($F_{2,57}$ = 6.081; p = 0.004). Increased intracortical inhibition in TMS single pulse suprathreshold stimulation (110%: $F_{2,57}$ = 6.842; p = 0.002; 130%: $F_{2,57}$ = 4.900; p = 0.011; 150%: $F_{2,57}$ = 4.638; p = 0.014; 170%: $F_{2,57}$ = 9.845; p < 0.001) and paired pulse protocols was also seen (SICI: $F_{2,57}$ = 23.390; p < 0.001, and LICI: $F_{2,57}$ = 21.603; p < 0.001). Using non-invasive stimulation techniques, this novel study showed increased cortical inhibition and compromised central information processing, suggesting neural mechanisms underpinning ongoing fatigue, allowing for potential clinical rehabilitation strategies. **© 2019 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: post concussion symptoms, fatigue, transcranial magnetic stimulation, somatosensory, vibrotactile, self-assessment questionnaire.

INTRODUCTION

Mild traumatic brain injury (mTBI) is the most common form of brain injury experienced by children and adults (Finch et al., 2013). Across the brain injury spectrum, concussion has been described as a subset of mTBI (Finch et al., 2013). However, concussion is characterized by a rapid onset of non-specific, transient signs and symptoms (Ropper, 2008). While microstructural neuropathology may occur, current clinical neuroimaging shows absence of any structural damage, thereby defining concussion as a 'functional' injury (Dimou and Lagopoulos, 2014; McCrory et al., 2017). In the majority of individuals, signs and symptoms resolve rapidly; usually within seven to 10 days (McCrory et al., 2017). However, it has been well described that a small but noticeable cohort (~10%) of individuals following concussion, continues to experience persistent lingering effects that may continue for months, and are recognized as post-concussion symptoms or PCS (Ryan and Warden, 2003; Guinto and Guinto-Nishimura, 2014).

Similar to concussion, there is a constellation of symptoms ascribed to PCS. These include: headaches, vertigo/dizziness, irritability, emotional labiality or irritability, cognitive difficulty (e.g., concentration), sleep disturbance and/or depression and anxiety (Broshek et al., 2015). However, persistent mental fatigue is one of the most long-lasting symptoms following a concussion. Yet despite this, it is often under-acknowledged (Johansson and Rönnbäck, 2014). A suggested reason for this is due to the disparity of self-reported fatigue in previous studies, ascribed to operational definitions and study methodological

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differences (Johansson and Rönnbäck, 2014). For example, in longitudinal studies the frequency of continually feeling tired (Johansson and Rönnbäck, 2012) in post concussed individuals varies from 16% to 73% of the sample studied (Van der Naalt et al., 1999; Stulemeijer et al., 2006; Johansson and Rönnbäck, 2012). Further, no correlation has been reported between complaints of severity of mental fatigue and severity of the initial injury, age of the person at the time of the injury, or time since the injury (Belmont et al., 2006; Johansson and Rönnbäck, 2014). Notwithstanding this lack of evidence, there is consensus that persistent fatigue has a meaningful impact on the individual's daily activities (Johansson et al., 2009; Johansson and Rönnbäck, 2012, 2014).

It is acknowledged that PCS can involve various components of the sensorimotor system such as dizziness and loss of balance, blurred vision, and loss of strength (Lau et al., 2011; McCrory et al., 2017). These variables can be assessed using clinical test protocols in those with PCS. For example, dizziness and loss of balance can be tested with standing/walking/perturbation assessments (McCrory et al., 2017). Vision can be assessed via oculomotor and nystagmography (Ventura et al., 2015; McCrory et al., 2017); while strength and physical effort can be tested using dynamometry (Greiffenstein et al., 1996; Crow et al., 2010). Despite this, assessing PCS individuals with ongoing fatigue has traditionally been challenging. Individual's self-reported responses are open to the subjective perceptions of their fatigue and to the interpretation by the clinician. Further, as time progresses, the severity of symptoms, such as those described above, declines to pre-injury levels, as well as neurocognitive testing scores regressing to the mean (De Kruijk et al., 2002; French et al., 2014). As a result, the individual's results may appear 'normal' (asymptomatic) during a clinical assessment (Rau et al., 2017). Studies have shown, however, that those with ongoing fatigue complaints show decreased processing speed and impaired ability to maintain attention during test administration, leading to frustration by the participant (Johansson et al., 2009). But it has been reported that such observations have been misrepresented by clinicians as the patient having a low-tolerance in completing such tasks (Mateer and Sira, 2006). Therefore, further study to objectively assess the effects of ongoing fatigue in PCS is required. One area that may provide evidence is the corticomotor pathway.

The difficulty in assessing an individual with PCS highlights the need to develop reliable physiological biomarkers in quantifying underlying mechanisms contributing to PCS fatigue. Previous studies have reported on electrophysiological changes, using (EEG or qEEG) with PCS (Duff, 2004). However transcranial magnetic stimulation (TMS) is unique given the technique has the capacity to quantify corticomotor excitatory and intracortical inhibitory synaptic potentials, via motor evoked potentials (MEPs), driven by neurotransmitter activity, allowing for understanding of neurophysiological mechanisms in context with functional observation assessments (Hallett, 2000; Kobayashi and Pascual-Leone, 2003; Pearce and Maller, 2018). Since 1985, TMS has been demonstrated to be a reliable technique in measuring cortical physiology in both health and disease (Hallett, 2000; Kobayashi and Pascual-Leone, 2003).

Across a range of conditions, TMS has demonstrated the ability to detect abnormalities in cholinergic transmission and long-term potentiation-like plasticity. Pharmacological interventions, such as the non-*N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine, have shown the increases in MEP excitability, inferring increased cortical excitability. Conversely, intracortical measures such as the cortical silent period (cSP) from single pulse TMS, (Wilson et al., 1993a) and paired pulse paradigms including short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI) allow for the study of γ-aminobutyric acid (GABA) receptor activity (Wilson et al., 1993a; Hanajima and Ugawa, 2008). For example, alterations in cSP duration have been observed in a range of acute and chronic concussion studies (see systematic review by Major et al. (2015)). Recent studies have utilized SICI and LICI measures in retired contact sport athletes with a history of concussion injuries (Pearce et al., 2014, 2018). To date, however, TMS has not been used to quantify those with PCS.

Similarly, vibrotactile stimulation provides an opportunity to quantify changes in central information somatosensory processing for the study of various neurological conditions (Holden et al., 2012). The topographic organization of the somatosensory system provides an optimal environment for evoking cortico-cortical interaction in near-adjacent regions (Tommerdahl et al., 2016) Indeed, a key concept in this model is that alterations in sensory perception, via specific stimulation paradigms detected in the fingertips, occur in parallel with alterations in systemic cortical alterations (Tommerdahl et al., 2016) including pharmacological manipulation (Folger et al., 2008), aging (Zhang et al., 2011a), migraine (Nguyen et al., 2013), and chronic pain (Zhang et al., 2011b). Vibrotactile assessment has also shown central information processing alterations in somatosensory processing in the acute phase following concussion (1–3 days post injury) (Tommerdahl et al., 2016) as well as quantifying physiological recovery from concussion between 18 and 48 days (King et al., 2018). Altered perception with amplitude discrimination (which stimulus is of a greater intensity), duration discrimination (which stimulus is presented for longer time) and time order judgment have been interpreted to represent physiological changes in GABAergic and/or NMDA receptor activity (Folger et al., 2008). Similar to TMS, somatosensory stimulation has not been utilized to measure those with ongoing symptoms analogous to PCS.

This is the first study to investigate the neurophysiological mechanisms, via evoked potentials and somatosensory stimulation, in those with PCS. A physiological multi-modality approach utilizing both vibrotactile and transcranial stimulation assessments was undertaken specifically focusing on PCS individuals with ongoing fatigue. Fatigue is often overlooked or neglected in assessment, (Johansson and Rönnbäck, 2014) but has been argued to have a notable impact on the somatosensory and motor systems, (Kuppuswamy, 2017) allowing for a unique opportunity for study. Therefore, the

aim of this novel investigation was to compare three groups: 1) Those with ongoing fatigue with diagnosed PCS; 2) Those who had previously had a concussion injury with full recovery; and 3) An age-matched control group with no history of head trauma. We hypothesized that those with ongoing PCS would demonstrate alterations in cortical inhibition with TMS protocols (cSP, SICI and LICI), and also differences in somatosensory assessment (reaction time and variability, amplitude discrimination, time order judgment, duration discrimination) when compared to those with a full recovery following concussion and controls.

EXPERIMENTAL PROCEDURES

The University Institutional Review Board prior to recruitment, conforming in accordance with the Declaration of Helsinki, approved all protocols. Recruitment of study participants (n = 60; based on significant intracortical inhibition changes, and moderate effect sizes from previous studies (De Beaumont et al., 2009; Pearce et al., 2014, 2018)) was undertaken after public announcements, highlighting the study and calling for volunteers. General inclusion criteria for all participants were to be over the age of 18 years and apart from concussion injury, were free of neurological or psychiatric disorders. Exclusion criteria included previously suffering a moderate or severe TBI, skull fracture, blast or overpressure brain injury, and currently involved in litigation relating to their concussion injury resulting in PCS. Prior to testing, all participants provided written informed consent and were pre-screened for suitability to TMS. All testing procedures were completed in one laboratory visit taking approximately 60 min. Participants in the PCS and recovered groups all self-reported experience at least one concussion injury that was diagnosed by a medical practitioner (Table 1). Concussions ranged from injuries on the sports field, workplace or in the home environment.

Inclusion for PCS required participants (n = 20; 36.1 ± 14.0 yr., 4 female) to be a minimum of 3 months (American Psychiatric Association, 2013) (mean of 15.4 ± 7.6 months) post-concussion injury and have had a medical professional diagnose them with PCS. Loss of consciousness (LOC) was reported in 55% of participants. In the remaining 45% LOC was less than 30 min. 60% of participants were taken to emergency for assessment, with one participant hospitalized for 3 days. Employment status included 65% working full-time, 20% working part time, and 15% reported being students or retired. No participants in this group reported using psychoactive recreational substances, and five of the 20 in this group were on prescribed medications for depression.

Participants (n = 20; 33.8 ± 6.6 yr., 2 female) who had fully recovered from a concussion (mean time post-concussion 12.9 ± 6.6 months) with no ongoing symptoms, and medical clearance to undertake all daily activities (Rau et al., 2017) were included in a comparison group. In this group, LOC was reported in 45% of participants. In the remaining 55% LOC was less than 30 min. 35% of participants were taken to emergency for assessment, with one participant hospitalized for 5 days. Employment status included 65% working full-time, 15% working part time, and 20% students or retired. No participants in this group reported using psychoactive recreational substances or were on prescribed medications.

Both PCS and recovered groups were compared to age, education and gender matched control group (n = 20; 37.7 ± 8.0 yr., 3 female), recruited from the general community, with no history of concussion or use of psychoactive recreational substances. Employment status included 70% working full-time, 25% working part time, and 5% retired. Table 1 provides participants' demographics.

Self-report fatigue

All participants completed the 15-question self-assessment of fatigue (Johansson et al., 2009). The questionnaire asks the individual to respond to statements (four response options) that best describes difficulties they encounter with common daily activities. Questions were related to aspects such as intensity, frequency and duration of ongoing symptoms. Higher scores reflect greater severity. A rating of 0 corresponds to no concern, 1 indicates a minor issue, 2 indicates a pronounced issue, and 3 relates to maximal severity. The questionnaire also allows for the participant to score between the given alternatives (0.5, 1.5, 2.5) (Johansson et al., 2009). For further details regarding the questionnaire the reader is directed to Johansson and colleagues (Johansson et al., 2009; Johansson and Rönnbäck, 2012, 2014).

Somatosensory testing

Somatosensory assessment was undertaken by using a portable vibrotactile stimulation device (Brain Gauge, Cortical Metrics, USA) that does not simply reflect alterations in tactile perception, but rather differences in cortical information processing capacity (Holden et al., 2012; Tommerdahl et al., 2016). The device, a similar size and shape to a standard computer mouse, contains two cylindrical probes (5 mm diameter) positioned at the top of the device. These probes provided a light vibration stimulus, at frequencies

Table 1. Participant group details, including overall score of self-report fatigue (Johansson et al., 2009).

	Age (years) (mean ± SD)	Male/ female	Number of years of education (mean ± SD)	Previous diagnosed concussions (mean ± SD)	Time (months) since last concussion (mean ± SD)	Self-report fatigue total score (mean ± SD)
PCS	36.2 (± 14.0)	15/5	14.2 (± 2.6)	4.0 (± 3.0)	15.6 (± 7.6)	18.9 (±5.9)
Recovered	33.8 (± 6.6)	16/4	14.4 (± 2.3)	4.8 (± 2.6)	12.5 (± 6.6)	6.4 (± 7.2)
Control	37.7 (± 8.0)	16/4	15.3 (± 2.6)			2.8 (± 4.5)

PCS: post concussion syndrome. Asterisk ( ) indicates significant difference ($p < 0.05$).

between 25 and 50 Hz that is sensed by the participant's index (D2) and middle (D3) digits of their non-dominant hand, with the dominant hand responding to questions, via a computer mouse, in regard to the test stimulus. Participants completed a battery involving seven discrete tasks utilized in previous studies (Folger et al., 2008; Zhang et al., 2011a,b; Nguyen et al., 2013; Tommerdahl et al., 2016; King et al., 2018) for a combined testing time of approximately 25 min. For each task, a simple tracking procedure that utilized a two-alternative forced choice paradigm was used to determine an individual's difference limen (Tommerdahl et al., 2016). Familiarization was performed before each test for participant orientation, requiring correct responses on three consecutive training trials before commencing with the data acquisition portion of the test. Participants were not provided feedback or knowledge of the results during data acquisition (Tommerdahl et al., 2016).

Detailed protocols have been presented previously (Holden et al., 2012; Tommerdahl et al., 2016). Briefly, data quantified during somatosensory assessment included reaction time (responding as quickly as possible with the dominant hand when a pulse stimulus was provided to the non-dominant hand D2), amplitude discrimination (which digit, D2 or D3, felt a greater intensity of vibration), temporal order judgment (which digit, D2 or D3, felt a stimulus first), and duration discrimination (which of the two stimuli lasted for a longer time). The reaction time task was completed at the beginning and at the end of the test battery to measure differences in reaction time as well as variability in reaction time allowing for inference of fatigue.

Transcranial magnetic stimulation (TMS)

Using previously described methods (Wilson et al., 1993b; Pearce and Kidgell, 2009, 2010; Pearce et al., 2013), TMS was applied over the contralateral motor cortex with surface electromyography (sEMG) recording 500 ms sweeps (100 ms pre-trigger, 400 ms post-trigger; PowerLab 4/35, ADInstruments, Australia). The sEMG activity was recorded using bipolar Ag/AgCl electrodes, with an intra-electrode distance of 2 cm positioned over the first dorsal interosseous (FDI) muscle of the participant's dominant hand adhering to the Non-Invasive Assessment of Muscles (SENIAM) guidelines for sEMG (Hermens et al., 1999).

Active single pulse and paired-pulse MEPs were obtained using a MagPro R30 stimulator (MagVenture, Farum, Denmark) with a MC-B65 Butterfly Coil (MagVenture, Farum, Denmark). For reliability of coil placement participants wore a snugly fitted cap (EasyCap, Germany), positioned with reference to the nasion–inion and interaural lines. The cap was marked with sites at 1 cm spacing in a latitude-longitude matrix to ensure reliable coil position throughout the testing protocol (Pearce et al., 2000).

Following identification of the 'optimal site', defined as the site with the largest observed MEP, active motor threshold (aMT) was determined, during a controlled, low-level voluntary contraction of the FDI muscle at 10% of Maximal Voluntary Contraction (MVC). The aMT was identified by delivering TMS stimuli (5% of stimulator output steps, and in 1% steps closer to threshold) at intensities from a level below the participant's threshold until an observable MEP of at least 200 μV and associated cSP could be measured in at least five of 10 stimuli (Wilson et al., 1993a; Pearce et al., 2000). Stimulus–response curves for MEP excitability and cSP inhibition were completed using single pulse TMS of increasing intensities (Pearce et al., 2014). A total of 20 stimuli, in five sets of four stimuli, presented at random intervals between 8 and 10 s, were delivered at intensities of 110%, 130%, 150% and 170% of aMT (Pearce et al., 2013). A break of 30 s was provided after each set and after each intensity level.

Due to inter-individual variation in the MEP waveform (Pearce and Maller, 2018) normalization of the MEP amplitude between participants was completed via direct muscle responses (M-wave), obtained from the FDI muscle by supramaximal electrical stimulation (pulse width 1 s) of the median nerve under resting conditions (DS7A, Digitimer, UK) (Kidgell and Pearce, 2010). An increase in current strength was applied to the radial nerve until no further increase in amplitude was observed in the sEMG (M_{MAX}). To ensure maximal responses, the current was increased an additional 20% and the average M_{MAX} was obtained from five stimuli each separated by between 6 and 9 s (Kidgell and Pearce, 2010).

Single pulse MEPs, from active conditions, were measured from the peak-to-trough difference of the waveform and normalized as a percentage of M_{MAX} (Kidgell and Pearce, 2010). Corticomotor latency was calculated as the time between stimulation of the motor cortex to the onset of the MEP (Major et al., 2015). Duration of the cSP was calculated from the onset (deflection) of the MEP waveform to the return of uninterrupted EMG (Wilson et al., 1993a). Paired-pulse MEPs for short latency intracortical inhibition (SICI) was measured with the FDI at rest using an interstimulus interval (ISI) of 2 ms, conditioning stimulus of 80% aMT and a test stimulus of 130% (Pearce et al., 2014, 2015). Fifteen sweeps were delivered at random intervals between 8 and 10 s and SICI was expressed as a ratio of the paired-pulse MEP to the MEP measured also at 130% (McGinley et al., 2010; Pearce et al., 2014, 2015). Long intracortical inhibition (LICI) was quantified in the FDI of 100 ms with suprathreshold conditioning and test stimuli at 130% of aMT (Pearce et al., 2014).

Statistical analyses

All data were screened for normal distribution using Kolmogorov–Smirnov tests, and found to be normally distributed. Levene's tests for equal variances found that the assumption of homogeneity of variance was met with all somatosensory and TMS variables; therefore parametric testing where employed with equal variances assumed. For the mental fatigue questionnaire, where variables did not meet the criteria for the assumption of homogeneity, Welch test for unequal variances was applied. All dependent variables (participant characteristics, Brain Gauge and TMS) were compared using a one-way ANOVA or *t*-test (where

appropriate), except for somatosensory reaction time and reaction time variability. Due to the repetitive measure at the start and completion of the test battery, somatosensory reaction time and reaction time variability were compared using a mixed-model repeated measures ANOVA. Where ANOVA detected differences, post-hoc testing with Bonferroni correction (for equal variances) or Games–Howell (for unequal variances) was used. Values are presented as mean and 95% confidence intervals (CI) unless where specified. Correlations (Pearson's *r*) were performed between significant dependent variables. Cohen's *d* for small (≤0.2), medium (0.21–0.8) and large (≥0.81) (Cohen, 1988) effect size differences are presented between groups for TMS and somatosensory results. Alpha was set at $p \leq 0.05$.

RESULTS

Participants recruited completed all tests with no adverse effects. Group comparisons (Table 1) showed no difference in age ($F_{2,57} = 0.434$; $p = 0.650$); and between the two post-concussion groups there were no differences in time since their last concussion ($t_{38} = 0.579$; $p = 0.932$), or the number of previous concussions ($t_{38} = -0.049$; $p = 0.095$).

A significant difference ($F_{2,57} = 52.583$; $p < 0.001$) was found between groups for the total sum of scores for mental fatigue questionnaire (see Table 1). Post-hoc tests revealed that the PCS symptomatic group reported a significantly higher total sum score compared to the recovered ($p < 0.001$) and control groups ($p < 0.001$). No differences were observed between the recovered and control groups ($p = 0.165$).

Self-report items

Individual items in the self-report are shown in Fig. 1(a–d). In all items ANOVA revealed significant differences between groups ($p < 0.001$, except *24-h variation* [Welch's $F_{2,20.4}$; $p = 0.020$]). Post hoc analyses showed that the PCS group self-rating across each item was significantly higher compared to the recovered group and controls (all $p \leq 0.001$), except for *increased sleep* and *24-h variation in fatigue* where the PCS group was significantly different to the control group only ($p = 0.007$ and $p = 0.023$ respectively).

Somatosensory assessment

Reaction time measures at the beginning and the end of the test battery showed a significant difference by time interaction ($F_{2,57} = 4.214$; $p = 0.020$) indicating that the PCS

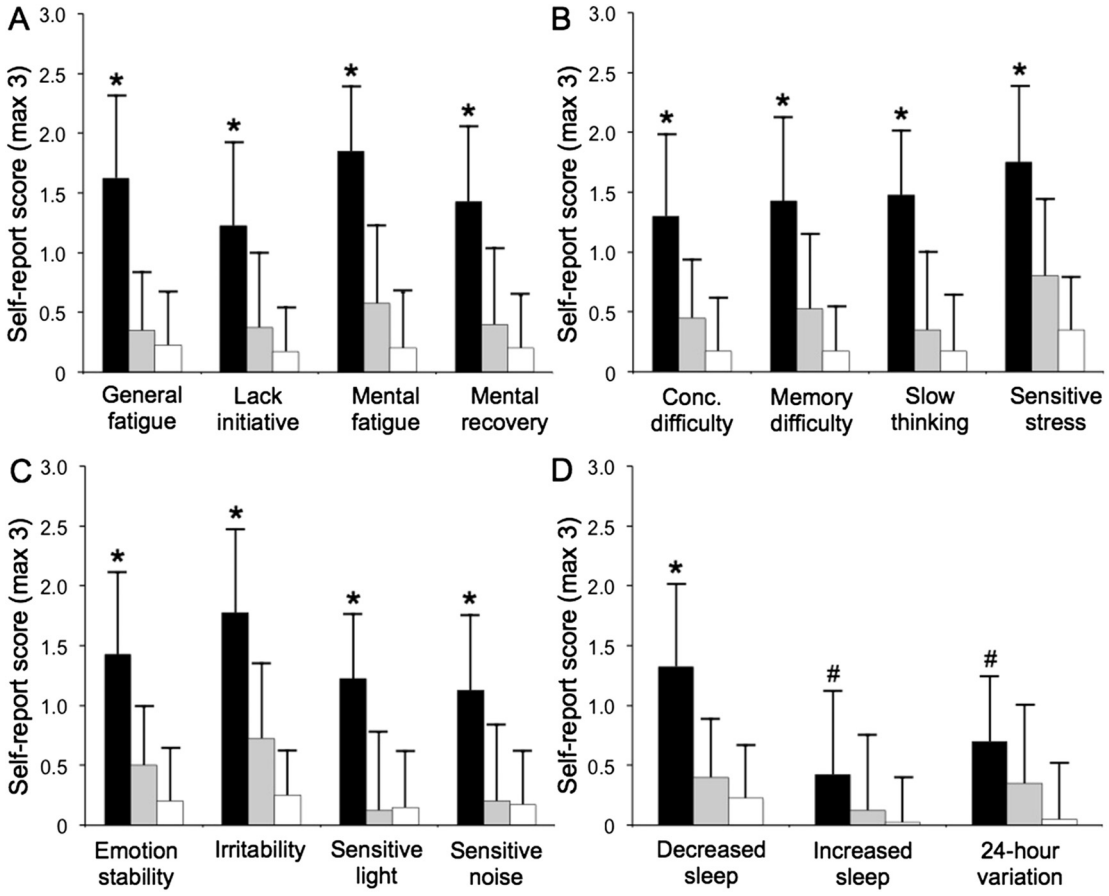

Fig. 1. (a–d) Mean (±SD) scores on self-report items between PCS (black bars), recovered concussion (gray bars) and controls (white bars). Asterisk (*) indicates post hoc significance between PCS group to recovered concussion and controls ($p < 0.05$); hashtag (#) indicates post hoc significance between PCS group and control only.

group, when compared to the recovered and control groups, performed poorly in the reaction times at the end of the test battery (see Table 2). Similarly, reaction time variability showed a significant difference by time interaction ($F_{2,57}$ = 5.505; p = 0.007) with the PCS group showing greater variability in reaction times at the end of the test battery when compared to the recovered and control groups. There were no differences observed in reaction time variability at the start and the end of the test battery for the recovered and control groups.

Between group differences were observed for amplitude discrimination ($F_{2,57}$ = 5.166; p = 0.009), temporal order judgment ($F_{2,57}$ = 4.606; p = 0.014) and duration discrimination ($F_{2,57}$ = 6.081; p = 0.004). Post hoc analyses showed that for each of these conditions, the PCS group was significantly worse than the recovered and control groups for amplitude discrimination (p = 0.03, d = 0.79 and p = 0.01, d = 0.87 respectively) and time order judgment (p = 0.04, d = 0.63 and p = 0.02, respectively). Duration discrimination showed no difference between symptomatic and asymptomatic groups (p = 0.06,d = 0.64), but significant differences were observed between symptomatic to controls (p = 0.004,d = 0.72).

Significant correlations were observed between self-report and somatosensory measures across all participants (n = 60). Total self-report scores showed high correlations with reaction time (r = 0.467; p < 0.001); reaction time variability (r = 0.502; p < 0.001); amplitude discrimination (r = 0.467; p < 0.001) and duration discrimination (r = 0.537; p < 0.001). Moderate correlations were found between total self-report score and time order judgment (r = 0.291; p = 0.02).

Transcranial magnetic stimulation

There were no significant differences observed for aMT ($F_{2,57}$ = 0.023; p = 0.977), or latency ($F_{2,57}$ = 1.214; p = 0.305; Table 3). Similarly, MEP amplitudes at all suprathreshold stimulus intensities did not show differences between groups (110%: $F_{2,57}$ = 1.577; p = 0.215; 130%: $F_{2,57}$ = 0.434; p = 0.650; 150%: $F_{2,57}$ = 0.815; p = 0.448; 170%: $F_{2,57}$ = 1.243; p = 0.296). While not statistically significant, moderate effect size differences (Cohen's d) where observed in MEP amplitudes at 150% (PCS vs. control: d = 0.27; Recovered vs. control: d = 0.37) and 170% (PCS vs control: d = 0.38; Recovered vs. control: d = 0.42; Table 3) above motor threshold (see Table 3). Conversely, intracortical inhibition measures all exhibited significant differences (110%: $F_{2,57}$ = 6.842; p = 0.002; 130%: $F_{2,57}$ = 4.900; p = 0.011; 150%: $F_{2,57}$ = 4.638; p = 0.014; 170%: $F_{2,57}$ = 9.845; p < 0.001) with post hoc analyses showing significantly increased intracortical inhibition (i.e. lengthened cSP) and associated large effect sizes (d range 0.79–1.0), in the PCS group when compared to the recovered and control groups (Table 3). Examples of cSP differences between the three groups are illustrated in Fig. 2. Paired pulse inhibition measures showed significant decreased SICI ($F_{2,57}$ = 23.390; p < 0.001) and LICI ($F_{2,57}$ = 21.603; p < 0.001) ratios, with post hoc analyses

Table 2. Somatosensory variables between groups (mean ± 95% CI).

	Reaction time 1 (ms)			Reaction time 2 (ms)			Reaction time variability 1 (ms)			Reaction time variability 2 (ms)			Simultaneous Amplitude discrimination (μm)			Temporal order judgment (ms)			Duration discrimination (ms)		
		95% lower	95% higher		95% lower	95% higher		95% lower	95% higher		95% lower	95% higher		95% lower	95% higher		95% lower	95% higher		95% lower	95% higher
PCS	297.4	250.3	344.6	307.8 #	227.1	388.5	19.8	11.9	27.7	34.4 #	18.4	50.4	46.0	32.5	59.5	46.6	30.6	62.8	75.8	45.1	106.5
Recovered	246.7	219.4	274.0	221.8	202.5	241.3	13.2	9.4	17.2	13.0	7.8	18.2	31.3	23.7	38.9	27.3	12.1	42.6	57.4	41.5	73.2
Control	232.9	219.0	246.9	214.6	202.2	226.9	14.5	11.9	17.1	12.3	9.3	15.4	32.5	22.2	42.9	23.8	19.1	28.5	48.7	39.8	57.7

Note: Reaction time/variability 1 completed at the start of battery, reaction time/variability 2 completed at end of battery. Asterisk ( ) indicates significant difference between groups (one-way ANOVA with Bonferroni post hoc). Hashtag (#) indicates significant interaction effect (repeated measures ANOVA).

Table 3. TMS measures between groups (mean ± 95% CI).

	Group	Mean	95% lower	95% higher
Active motor threshold (% of max stimulator output)	PCS	35.6	33.3	37.9
	Recovered	35.8	31.8	39.8
	Control	35.4	32.7	38.1
Motor evoked potential latency (ms)	PCS	24.0	23.2	24.8
	Recovered	23.7	22.7	24.6
	Control	23.2	22.7	23.8
Motor evoked potential 110% (% of M_{MAX})	PCS	10.2	6.7	13.7
	Recovered	14.0	9.5	18.4
	Control	10.0	7.0	13.1
Cortical silent period 110% (ms)	PCS	78.25*	64.6	91.8
	Recovered	56.67	50.6	62.6
	Control	56.82	48.1	65.5
Motor evoked potential 130% (% of M_{MAX})	PCS	21.2	12.9	29.5
	Recovered	26.6	18.5	34.7
	Control	24.6	19.4	28.9
Cortical silent period 130% (ms)	PCS	127.3*	112.1	142.6
	Recovered	102.5	88.3	113.7
	Control	110.0	102.1	118.5
Motor evoked potential 150% (% of M_{MAX})	PCS	34.8	25.3	44.2
	Recovered	42.0	29.2	54.7
	Control	44.5	31.9	57.1
Cortical silent period 150% (ms)	PCS	156.6*	142.3	170.9
	Recovered	131.1	114.3	147.9
	Control	132.5	122.7	142.3
Motor evoked potential 170% (% of M_{MAX})	PCS	36.3	27.9	44.7
	Recovered	45.5	31.8	59.2
	Control	48.7	35.3	62.1
Cortical silent period 170% (ms)	PCS	183.4*	167.8	198.9
	Recovered	149.8	133.9	165.5
	Control	144.1	133.5	154.7
Short interval intracortical inhibition (ratio)	PCS	0.32*	0.28	0.37
	Recovered	0.52	0.44	0.60
	Control	0.59	0.54	0.65
Long interval intracortical inhibition (ratio)	PCS	0.43*	0.37	0.49
	Recovered	0.59	0.52	0.67
	Control	0.70	0.65	0.75

Note: (*) indicates significant difference between groups (one-way ANOVA with Bonferroni or Games-Howell post hoc).

showing the PCS group significantly reduced SICI ($P < 0.001$; $d = 1.54$ vs recovered; d = 2.68 control) and LICI ($P < 0.001$; $d = 1.13$ vs recovered; 2.11 control) ratios compared to the recovered and control groups.

There were notable correlations observed between the self-reported total score and intracortical inhibition. Moderate correlations were observed with cSP at 110% ($r = 0.37$; $p = 0.003$), 130% ($r = 0.38$; $p = 0.003$), and 150% ($r = 0.36$; $p = 0.005$). There were strong correlations observed with cSP at 170% ($r = 0.46$; $p < 0.001$), SICI ($r = -0.52$; $p < 0.001$) and LICI ($r = -0.50$; $p < 0.001$) when compared with fatigue self-reported total score. Correlations were observed between somatosensory and TMS variables. Reaction time and reaction time variability were correlated with cSP at 110% ($r = 0.54$; $p < 0.001$; $r = 0.44$; $p < 0.001$), 130% ($r = 0.29$; $p = 0.02$; $r = 0.28$; $p = 0.03$), 150% ($r = 0.34$; $p = 0.007$; $r = 0.26$; $p = 0.04$), 170% ($r = 0.34$; $p = 0.008$; $r = 0.26$; $p = 0.04$), and SICI ($r = -0.35$; $p = 0.005$; $r = -0.38$; $p = 0.002$). Interestingly, LICI was not significantly correlated with reaction time ($r = -0.09$; $p = 0.45$) and reaction time variability ($r = -0.21$; $p = 0.11$). There were significant correlations observed with amplitude discrimination and cSP at 110% ($r = 0.26$; $p = 0.04$), 130% ($r = 0.54$; $p = 0.02$), 150% ($r = 0.25$; $p = 0.04$), and 170% ($r = 0.38$; $p = 0.003$), as well as SICI ($r = -0.35$; $p = 0.006$), and LICI ($r = -0.29$; $p = 0.02$). Duration discrimination was also significantly correlated with cSP at 110% ($r = 0.35$; $p = 0.006$), 130% ($r = 0.39$; $p = 0.002$); 150% ($r = 0.41$; $p = 0.001$), and 170% ($r = 0.36$; $p = 0.005$) as well as SICI ($r = -0.41$; $p = 0.001$).

DISCUSSION

The prevailing view of PCS is that from the outset, neurobiological and psychological factors play a role in post-concussion symptoms (Silverberg and Iverson, 2011; Johansson and Rönnbäck, 2014; Broshek et al., 2015). Due to limited evidence however, as time progresses, mechanisms are less clear regarding persistent PCS (Silverberg and Iverson, 2011). Further, fatigue is not considered as a separate diagnostic entity, but rather defined within the diagnoses mild cognitive impairment, and post-traumatic brain symptoms (Organization, 1992; Johansson and Rönnbäck, 2014). The results in this study suggest that individuals with ongoing PCS have altered neurophysiology and central information processing. This finding suggests a

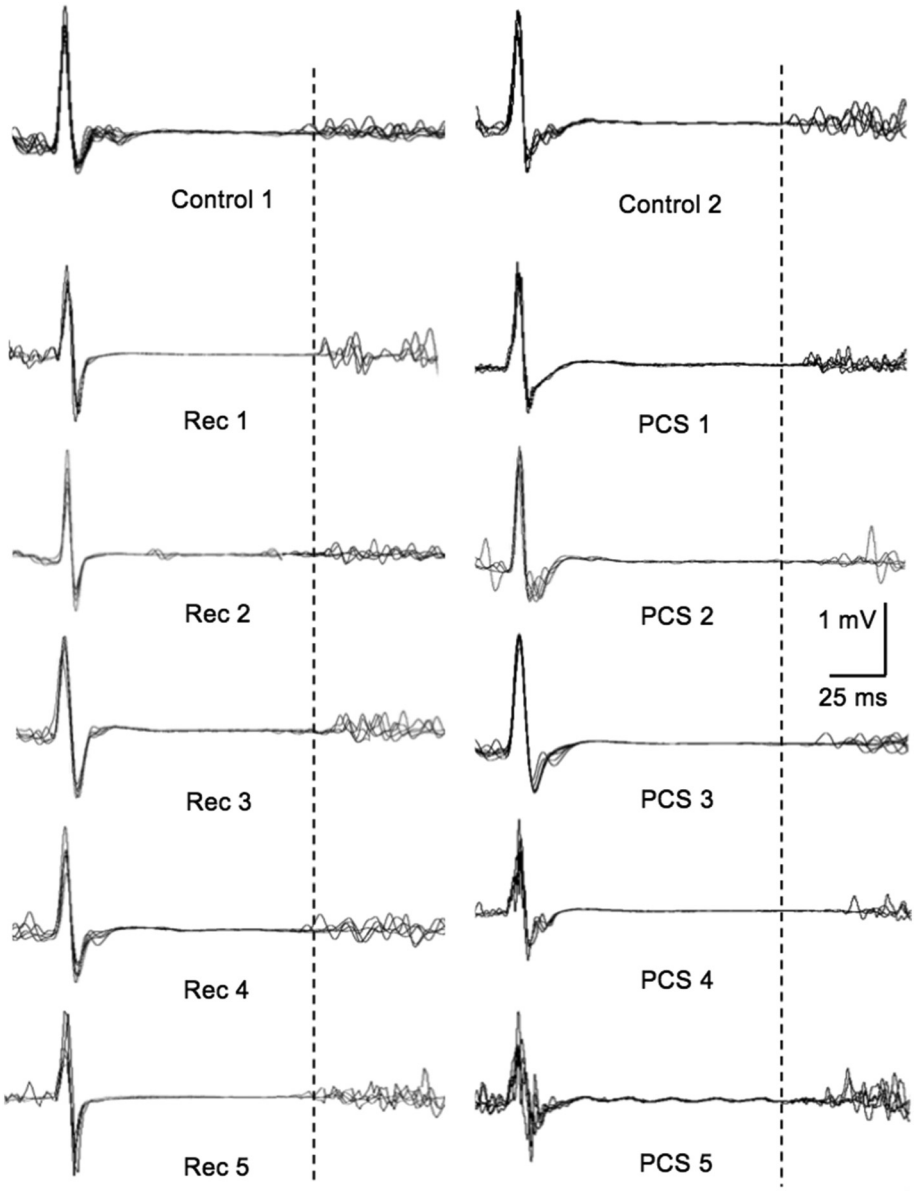

Fig. 2. Example of raw overlaid TMS sweeps (150% above active motor threshold) between control participants (top row) and five typical participants from the 'recovered' group (Rec1–Rec5) and five typical participants from the 'PCS' group (PCS1–PSC5). Dotted line represents ~130-ms group mean from control group to illustrate altered cSP duration in majority of PCS participants.

mechanistic explanation for PCS, particularly those with ongoing fatigue allowing for potential therapeutic interventions.

While the exact mechanisms of fatigue with PCS are still not fully known (Johansson and Rönnbäck, 2014), physiological hypotheses include abnormal neurometabolic functioning, such as down-regulation of astrocyte glutamate transporters and sodium/potassium ATPase activity (Rönnbäck and Hansson, 2004; Frencham et al., 2005; Rönnback and Johansson, 2012; Block et al., 2013; Johansson and Rönnbäck, 2014). Johansson and Rönnbäck (2014) have posited that if these physiological systems are not completely recovered following the injury, neural transmission will be impaired. Our study provides empirical evidence of altered central neural transmission via TMS and somatosensory assessment. The components of the MEP, waveform amplitude and cSP, represent post-synaptic cortical excitability and pre-synaptic intracortical processes (Bestmann and Krakauer, 2015). Particularly at high MEP amplitudes, it has been postulated that neurotransmitters such as glutamate and γ-aminobutyric acid (GABA), and neuromodulators (dopamine, norepinephrine, serotonin and acetylcholine) alter MEP waveform size (Ziemann, 2013). However, although using a low-level tonic contraction during stimulation has demonstrated reliability and validity in the MEP (Pearce and Maller, 2018), differences between groups should still be interpreted with caution due to inter-individual variability in the waveform amplitude.

Conversely, significant correlations were observed with intracortical inhibition measures for cSP, SICI and LICI when compared to self-reported fatigue, and somatosensory measures for reaction time, reaction time variability, amplitude and duration discrimination. Altered MEP waveforms have previously been demonstrated in those with other persistent fatigue conditions (e.g. myalgic encephalomyelitis or major depressive disorder) where studies have demonstrated abnormal intracortical inhibition, and/or reduced motor cortex excitability, which are posited to GABAergic receptor activity (Brouwer and Packer, 1994; Sacco et al., 1999; Starr et al., 2000; Steele et al., 2000). While we screened all participants for other neurological and psychiatric disorders, such as myalgic encephalomyelitis (ME) or major depressive disorder (MDD), we relied on self-report that participants in the PCS group were only diagnosed with PCS without comorbidities such as MDD or ME. The overlap of clinical symptoms between MDD and PCS is acknowledged, as well as TMS studies showing increased intracortical inhibition in those with MDD (Steele et al., 2000). Therefore further studies are required to tease out neurophysiological correlates between those with PCS and MDD, in order to measure the diagnostic efficacy of TMS for PCS assessment.

The correlation of increased intracortical inhibition when compared with amplitude discrimination is notable. While a

number of concussion studies utilizing TMS have reported alterations in cSP duration suggesting GABAergic activity changes (Major et al., 2015), somatosensory studies have similarly inferred altered GABA activity as a mechanism contributing to poorer discriminative ability in those who have been acutely concussed, when compared to controls (Tommerdahl et al., 2016). Further, while the correlations between TMS intracortical inhibition and slowed reaction times have previously been observed in chronic manifestations of repeated head trauma, several decades after the individual's last concussion, (De Beaumont et al., 2009, 2013; Pearce et al., 2014; Pearce et al., 2018) this is the first study to present worsening of reaction times *and* reaction time variability associated with increased TMS intracortical inhibition in this cohort. As a result, further studies should investigate reaction time variability in this cohort.

In this study, we have provided the first data utilizing techniques that were non-invasive and relatively inexpensive, allowing for the possibility of employing these technologies in a clinical setting. While the potential for clinical utility is promising, allowing for objective biomarker measures to compliment clinical assessment, this study was limited by focusing comparison on a particular sub-group within the constellation of symptoms experienced by those with persistent PCS. Therefore caution is required to generalizing these findings to the wider PCS cohort. Further studies are therefore required to better understand the neurophysiological nature of PCS more generally, comparing those with various levels of fatigue and those who complain of symptoms more so than fatigue. Future studies need to also investigate the diagnostic efficacy of paired-pulse TMS paradigms (including intracortical facilitation) in assisting the clinical assessment, such as recent studies demonstrating abnormal intracortical inhibition for clinical diagnosis of Alzheimer's disease (Motta et al., 2018; Padovani et al., 2018).

In conclusion, the novel data presented in this study provide the first lines of evidence suggesting abnormal GABAergic activity in those suffering with persistent PCS fatigue compared to individuals who have recovered from a concussion, and age-matched controls. Using non-invasive TMS and somatosensory techniques provides a new insight into central nervous system information processing mechanisms that can assist the clinical assessment challenges in diagnosing and rehabilitating those with PCS.

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