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# Implementing a structured exercise program for persistent concussion symptoms: a pilot study on the effects on salivary brain-derived neurotrophic factor, cognition, static balance, and symptom scores

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## ABSTRACT

**Primary objective:** Persistent concussion symptoms (PCS) affect 10–30% of individuals after sports-related concussion. This study evaluated the effect of exercise-based rehabilitation on symptom scores, brain-derived neurotrophic factor (BDNF), cognitive functions and static balance in a sample of participants with PCS.

**Research design:** One group pre-test post-test pilot study.

**Methods and procedure:** Nine participants with PCS received a structured exercise-based rehabilitation program. Changes in symptom scores, BDNF, cognitive functions and measures of static balance were used to evaluate the utility of the exercise program.

**Main outcome and results:** The results of this pilot study indicate a significant improvement in symptom scores following treatment, as well as some associated benefits in regards to cognitive function and static balance. BDNF levels in the participants with PCS within this study are notably lower than in a previous study on healthy controls.

**Conclusions:** The preliminary evidence reported in the current pilot study is clinically relevant as our findings suggest exercise-based treatments may improve PCS outcomes in a more favourable manner than rest-based treatment.

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## KEYWORDS

Persistent concussion symptoms; sports-related concussion; active rehabilitation; neuroplasticity; brain-derived neurotrophic factor

## Introduction

The majority of sport-related concussions will spontaneously resolve within a period of 10–14 days for adults, and four weeks for children (1–4). In 10–30% of cases, sport-related concussions may develop persistent concussion symptoms (PCS) which may take weeks, months or even years to resolve (5,6). The Berlin Concussion Consensus Guidelines stated that PCS be used as a term to describe symptoms following a concussion that have not reached clinical recovery within a period of 10–14 days in adults, and greater than four weeks in children (2). The cause of PCS is not due to any one pathophysiological dysfunction, rather a collection of non-specific symptoms that may be associated with coexisting and/or comorbid factors (2). These coexisting and comorbid factors may result in PCS without any underlying physiological brain dysfunction. In order for an individual with PCS to be considered clinically recovered, he/she must have returned to normal activities such as school, work and sport (2). Although a subject with PCS may achieve clinical recovery, evidence of lingering neurobiological injury has been documented in the form of damaged grey and white matter tracts within the central nervous system (7). This neurobiological damage may result in impaired cognitive functions observed

in individuals suffering from PCS for durations of several months or greater than a year. Recently, a potential PCS classification system was proposed to stratify individuals with PCS into one of three post-concussion disorder (PCD) subgroups: physiologic PCD, vestibulo-ocular PCD and cervicogenic PCD (8). Ellis et al. (8) suggested that a comprehensive clinical history, physical examination and exercise testing using the Buffalo Protocol allowed researchers and clinicians to gain a better insight into what underlying impairments may be contributing to PCS. Therefore, with an improved idea of what may be causing lingering symptoms, rehabilitation strategies can be tailored to the individual to best address his/her symptoms (8).

In the acute phase of sport-related concussion there is a consensus that cognitive and physical rest is the best course of action. According to the Berlin Consensus Guidelines, this period of rest should range from 24–48 hours (2) but the ideal length for the rest period is still not well understood. Until these recent guidelines, cognitive and physical rest was also recommended for PCS, despite limited literature to support this treatment approach (3). For those with PCS, a period of prolonged rest could possibly result in physical deconditioning, the development of PCS comorbidities, and/or socio-economic stress (9,10). Exercise too soon after a concussion,

without an adequate period of cognitive and physical rest, can result in symptom exacerbation and impaired regenerative neuroplastic processes (6,11,12).

Recent evidence indicates that following a period of rest, there may be a potential benefit of administering sub-symptom threshold aerobic exercise as a means to improve PCS, specifically symptoms associated with physiologic PCD (2,13–17). Concussion may result in a desynchronization between the autonomic nervous system and cardiovascular system, manifesting clinically as impaired regulation of cerebral blood flow (CBF) and heart rate variability (HRV) (11,18,19). Furthermore, under typical circumstances CBF is tightly associated to neuronal activity and brain metabolism (20). Therefore, it could be possible that disrupted blood flow and heart rate (HR) regulation may be responsible for headache and exercise intolerance; while impaired glucose metabolism may result in cognitive fatigue and difficulty concentrating. Aerobic exercise has been extensively documented to improve autonomic regulation in regards to CBF and HRV, while also profoundly benefitting multiple aspects of cognitive function (21–27). Moreover, aerobic exercise has been documented to improve neuroplasticity; the ability of neurons to alter the strength and efficacy of pre-existing synapses, in addition to forming new synaptic connections (12,23,24,28,29). This formation of new synapses can also extend to include the regeneration of synapses following a central nervous system injury (i.e., concussion). Neurotrophic factors are a family of proteins documented to contribute to the regulation of neuronal survival, development, function and plasticity (30). Of the neurotrophic factors, brain-derived neurotrophic factor (BDNF) plays a key role in regulating neuroplasticity and its known functions demonstrate potential as a non-pharmacological intervention to benefit impaired neurological abilities (31). BDNF can be measured and collected either through blood serum or saliva samples. Decreased levels of BDNF have been reported in neurodegenerative diseases such as Alzheimer's Disease and Huntington's Disease; as well as in neuropsychiatric conditions such as depression and schizophrenia (32). The administration of aerobic exercise to human subjects and animal models with traumatic brain injury, Alzheimer's Disease and stroke has resulted in notable improvements in aspects of cognitive function such as reaction time, memory and learning (28,33,34). The improvements observed in these studies were strongly associated with increased BDNF concentrations in response to the aerobic exercise programs. Aerobic exercise has been reported to prime the nervous system to undergo plastic changes to achieve the desired behaviour change (34). Therefore, increasing BDNF may facilitate the internal environment to allow the brain and central nervous system to heal itself while experiencing PCS. This enhanced neuroplasticity may result in improvements in underlying neurobiological injury, as well as clinically, in the form of improved memory, learning and concentration. In addition, aerobic exercise promotes recovery from depression and has been documented to be as potent as serotonergic medications (35). Depression is known to be a confounding factor for the progression of PCS; consequently, known benefits of aerobic exercise may address several different aspects of PCS as listed above (2).

Following concussion, balance disturbances are among the most common symptoms reported (36). Although balance

deficits appear to resolve quickly in the majority of cases, if the function and/or sensory integration of the visual or vestibular systems are impaired due to concussion, abnormalities in balance may persist for weeks or months (37,38). Vestibular rehabilitation has shown promise as an effective intervention for persons with persistent dizziness and/or balance impairments following concussion (39). Furthermore, Alsalaheen et al. (39) reported that the implementation of gaze stabilization exercises, standing balance and walking with balance challenges produced significant improvements in self-report and clinical balance performance measures.

In the case of PCS, the rationale for the implementation of active exercise-based treatment is four-fold. First, active exercise-based treatment may result in improved autonomic regulation and restoration of normal CBF and HRV, in addition to restoring cardiovascular fitness. Second, improved BDNF concentrations via aerobic exercise may facilitate neuroplasticity, resulting in improved cognitive function and healing of neurobiological injury. Third, active exercise-based treatment may improve symptoms of depression, which are considered contributors to PCS. Last, balance retraining exercises may restore normal balance abilities reducing the risk of a fall that may cause yet another concussion. Based on this rationale, the purpose of this pilot study was to investigate the feasibility of providing a 12 session structured and supervised sub-symptom threshold aerobic and balance exercise (AEB) program, and examining the program's effect on salivary-BDNF levels, cognitive function, balance and symptom scores in individuals diagnosed with PCS.

## Methods

### Design

After obtaining ethical approval from the academic institution ethics board, a one group pre-test post-test design was implemented. The effect of a supervised and progressive AEB retraining program was evaluated in nine participants with PCS across eight dependent variables. The dependent variables included: resting HR; resting blood pressure (BP); salivary-BDNF concentrations; Immediate Post-Concussion Assessment and Cognitive Testing (ImpACT) battery visual memory composite score, verbal memory composite score, visual motor speed composite score, and reaction time composite score; changes in average velocity of centre of pressure (COP) and COP path length during the Balance Error Scoring System (BESS); and Post-Concussion Symptom Scale (PCSS) scores.

### Subjects

Nine subjects diagnosed with PCS who had been experiencing lingering symptoms of concussion participated in this study. All participants were actively engaged in competitive sports such as: ice hockey, American football, soccer, volleyball, tennis and cheerleading. Eight participants suffered concussions while competing in his/her respective sport, or during gym class at school. One participant suffered his concussion in a car accident. Individuals who sustained a concussion were included in the study if he/she met the

following criteria: were males or females between the ages of 14 and 30 years; sustained a concussion in which the symptoms did not resolve within the first 10 days and persisted a minimum of eight weeks after the initial injury; were diagnosed with PCS by a physician; and were cleared to begin light exercising by his/her physician. Conversely, individuals were excluded from participation if they: presented with headache pain that was associated with migraine headache; had been diagnosed with depression or other mental health disorders; had attention deficit hyperactivity disorder, learning disabilities or sleep disorders prior to sustaining the head injury resulting in PCS; and sustained a concussion but all symptoms resolved in less than eight weeks.

Participants who partook in the study were referred from the academic institution's concussion clinic. The physician determined if the potential participant with PCS was cleared to engage in light physical activity. Individuals who met the inclusion criteria were identified and informed of the study by the referring physician. Informed consent/assent was obtained from prospective participants and/or legal guardians. Upon receiving informed consent, the data collection process consisted of three distinct components: (1) Initial (pre-treatment) assessment; (2) 12 session AEB program and concussion education and (3) Post-treatment assessment.

### Assessment protocol and treatment program

The initial assessment began with the collection of a saliva sample in order to measure salivary-BDNF concentrations. Salivary-BDNF was collected and processed as previously described (40–42). Briefly, saliva was collected via passive drool, processed, and stored at  $-80^{\circ}\text{C}$  until analysis after all post-treatment samples were collected. Salivary-BDNF concentrations were quantified using a sandwich Enzyme-Linked Immunosorbent Assay (ELISA) using recombinant BDNF as a standard. Next, participants completed the ImPACT battery in order to assess neurocognitive function. The ImPACT battery provided a standardized method of assessing participant verbal memory, visual memory, visual motor speed and reaction time. The PCSS is embedded within the ImPACT battery, so this was completed at the same time as well. Last, participants completed a Balance Error Scoring System (BESS) protocol on an Advanced Mechanical Technology, Inc. force platform to assess static balance. The BESS protocol included three testing positions: (1) Double leg stance (DS) with the feet touching (side by side), and their hands on his/her hips with their eyes closed; (2) Single leg stance (SL), standing on the non-dominant leg with their hands on his/her hips, and their eyes closed and (3) Tandem stance (TS), standing with the toes of the non-dominant foot touching the heel of the dominant foot, their hands on his/her hips, and their eyes closed. Testing consisted of one trial in each of the described positions on a firm surface, followed by one trial in each testing position standing on a foam pad, for a total of six trials lasting 20 seconds each. The BESS protocol was not scored and only the positions were used as a standardized method to assess static balance. Force platform data was collected and extracted to evaluate the average velocity of centre of pressure (COP), as

**Table 1.** Exercise parameter progression template.

	Sessions 1, 2, 3	Sessions 4, 5, 6	Sessions 7, 8, 9	Sessions 10, 11, 12
Aerobic HR reserve (%)	20	30	40	50
Aerobic duration (mins)	25	30	35	40
Balance duration (seconds)	15	15	20	20
Balance surface	Firm	Foam	Firm	Foam
Balance vision	Eyes open	Eyes open	Eyes closed	Eyes closed

well as the length of the path of COP during the BESS protocol.

After completion of the initial assessment, participants attended 12 one-hour AEB training sessions over the course of approximately four weeks (three sessions per week). The 12 sessions began with a warm-up followed by, stationary cycling, static balance training, and then cool down exercises requiring approximately 40–60 minutes for each session. All sessions were supervised and guided by a Canadian Society of Exercise Physiology Certified Personal Trainer (CPT). A HR monitor (Polar FT2 HR Monitor, Polar, Inc., Kempele, Finland) was worn by participants for the whole duration of each session to maintain the intensity of exercise at a pre-determined exercise HR. Sessions began with a five-minute warm-up on a stationary cycle ergometer (Monark 828E Ergometer, Monark Exercise, Vansbro, Sweden) at a self-selected speed and resistance until he/she achieved their respective target HR for the session. Heart rate intensity was calculated using the Karvonen formula:

$$\text{Target Exercise HR} = ((220 - \text{Age} - \text{Resting HR}) \times \% \text{Intensity}) + \text{Resting HR}$$

The Karvonen method was selected as it individualizes exercise intensity for each individual based on his/her HR reserve (43). Aerobic and balance exercise was progressed throughout the 12 session AEB program following the exercise parameter template summarized in Table 1.

The supervising CPT checked the participant's HR every two minutes to ensure he/she was within the desired exercise intensity. If the participant noted an exacerbation in any one of his/her concussion symptoms, he/she was instructed to stop cycling, and no further exercise was administered on the same day. The HR at which his/her symptoms were exacerbated was recorded. If this occurred, the intensity of the aerobic exercise component during the next exercise session was adjusted based on the HR recorded at symptom exacerbation. Following the aerobic component of each session, participants had a five-minute rest period before performing three sets of balance exercises. The balance exercises included the same three positions performed during the BESS protocol; DS with feet side by side and touching; SL while standing on one leg; and TS with the heel of one foot directly in front of the toes of the other foot. Participants completed three sets of each exercise, with a one minute rest between each exercise. The difficulty of balance exercises was progressed over the span of the 12 sessions by increasing the duration, manipulating the surface participants stood on from firm ground to soft foam, and manipulating whether their eyes were open or closed while balancing. Following the conclusion of all exercise

sessions, participants completed a post-treatment assessment in the exact same manner as the initial assessment.

### Data analysis

Statistical analysis was completed using IBM SPSS 20 for Windows. Descriptive statistics were calculated in order to provide the mean and standard deviations for the variables of interest. Statistical significance was examined using Paired Samples T-Tests for changes in pre- to post-treatment for each of the dependent variables: resting HR; resting systolic BP; resting diastolic BP; salivary-BDNF concentrations; ImPACT battery visual memory composite score, verbal memory composite score, visual motor speed composite score, and reaction time composite score; changes in average velocity of COP and COP path length during the BESS; and PCSS scores. A Bonferroni correction was applied to the measures of COP to minimize type I error. The alpha level was set at  $p < .05$  for all tests. Additionally, a log transformation correlation between pre-treatment salivary-BDNF concentration and the fold change due to treatment was conducted.

### Results

Nine participants with PCS participated in the study. A mean of 99.88 days (SD  $\pm$  79.95) elapsed from the date of participant's initial concussion, before being recruited into the study. The mean number of days to complete the AEB program was 36.78 ( $\pm$  11.85), with a minimum of 20 and a maximum of

60 days. This variability and wide range was increased due to the limited availability of some of the participants. The demographic findings and characteristics of the participants are presented in Table 2

There were no statistically significant differences for resting HR, resting systolic BP, resting diastolic BP, or for salivary-BDNF concentrations following the AEB program. Individual changes in salivary-BDNF concentration levels were notably variable across the nine participants and are summarized in Figure 1. Interestingly, participant six completed the AEB treatment in 20 days and exhibited the greatest improvement in salivary-BDNF levels. In contrast, participant five required 60 days to complete the AEB program and exhibited the lowest concentration of salivary-BDNF levels post-treatment. A log transformation correlation (Figure 2) revealed a statistically significant relationship ( $p = 0.04$ ,  $r^2 = 0.45$ ) indicating that 45% of the variance in the salivary-BDNF concentration fold-change was explained by pre-treatment BDNF concentrations. Of the five participants with the lowest pre-treatment BDNF concentration, three of the five showed increases in salivary-BDNF. None of the four participants that began the treatment with the highest salivary-BDNF concentrations showed any increase following the AEB treatment. There was no significant difference in verbal memory, visual memory, or reaction time following the treatment. A statistically significant improvement in visual motor processing speed, however, was observed ( $t(8) = -2.56$ ,  $p = .03$ , 95% CI  $[-8.60, -0.45]$ ,  $d = -0.55$ ). There were no changes in the length of the COP path during the BESS protocol while performing DS firm, SL firm, TS firm, or TS

Table 2. Participant demographics.

Case	Age (years)	Gender	Height (cm)/Weight (kg)	Cause of PCS	Time before treatment (days)	Time in treatment (days)	Pre-PCSS score	Post-PCSS score
1	14	M	165/55	Hockey	90	35	14	1
2	14	F	154/54.5	Cheerleading	65	46	22	2
3	19	M	180/75	Car accident	668	28	78	91
4	17	F	170/58	Volleyball	64	31	26	10
5	14	F	160/59	Soccer	58	60	12	3
6	21	M	185/79.5	Hockey	115	20	13	2
7	18	F	163/58	Gym Class	51	43	45	8
8	15	M	188/132	Football	291	39	60	41
9	15	F	162/53	Soccer	65	29	28	4

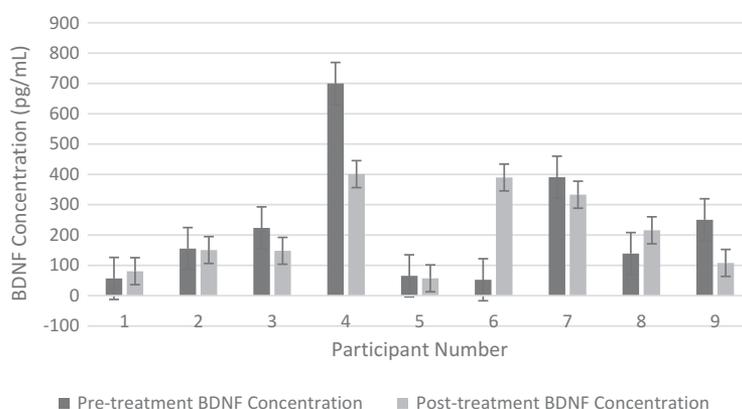
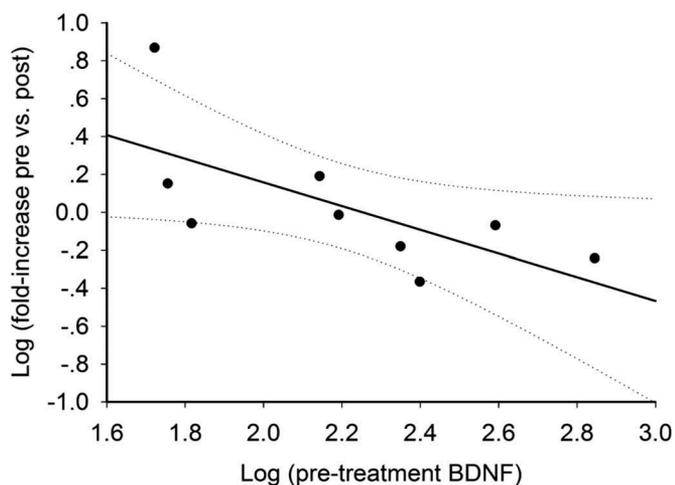


Figure 1. Salivary-BDNF concentrations pre- and post-treatment.



**Figure 2.** Log transformation correlation between pre-treatment salivary-BDNF concentration (pg/ml) and the fold change due to intervention.

foam stances. Conversely, significant improvements were observed in the length of COP path during DS ( $t(8) = 4.06$ ,  $p = .004$ , 95% CI [4.34, 15.80],  $d = 0.87$ ) and SL ( $t(8) = 3.80$ ,  $p = .005$ , 95% CI [4.62, 18.87],  $d = 0.66$ ) stances performed on the foam surface. There were no significant changes in regards

to the average COP velocity during the BESS protocol while performing the DS firm, SL firm, TS firm, or TS foam stances. Conversely, statistically significant improvements were observed in the average velocity of COP during the DS ( $t(8) = 4.06$ ,  $p = .004$ , 95% CI [0.22, 0.79],  $d = 0.88$ ) and SL ( $t(8) = 3.80$ ,  $p = .005$ , 95% CI [0.23, 0.94],  $d = 0.66$ ) stances performed on the foam surface. A statistically significant reduction in PCSS scores ( $t(8) = 3.37$ ,  $p = .01$ , 95% CI [4.77, 25.45],  $d = 0.56$ ) were also observed following treatment (see Table 3 for a summary of the findings).

## Discussion

The purpose of this pilot study was to investigate the feasibility of providing a 12 session structured and supervised sub-symptom threshold AEB program, and examining the program's effect on salivary-BDNF levels, cognitive function, balance and symptom scores in individuals diagnosed with PCS. The results of this pilot study reveal that implementing such a program is feasible and adds to the currently limited body of literature regarding the use of exercise as a treatment strategy for improving PCS.

After weeks or months of prescribed rest it was expected that participants within this study would be physically deconditioned, and this would manifest in the form of elevated

**Table 3.** Pre- and post-treatment changes at the group level.

	Pre-Intervention Mean $\pm$ SD	Post-Intervention Mean $\pm$ SD	<i>T</i>	<i>P</i>	Cohen's <i>d</i>
Physiological					
Resting HR	68.11 $\pm$ 2.99	66.56 $\pm$ 2.10	0.84	.43	-
Resting systolic BP	110.89 $\pm$ 1.87	110.78 $\pm$ 2.09	0.09	.93	-
Resting diastolic BP	70.11 $\pm$ 2.42	71.22 $\pm$ 2.01	0.42	.42	-
Salivary-BDNF concentrations	226.01 $\pm$ 69.63	209.33 $\pm$ 44.37	0.29	.78	-
Cognitive function (ImPACT)					
Verbal memory	75.56 $\pm$ 21.20	80.00 $\pm$ 21.72	-1.68	.13	-
Visual memory	63.22 $\pm$ 18.59	70.44 $\pm$ 18.37	-1.73	.12	-
Processing speed*	29.62 $\pm$ 7.85	34.15 $\pm$ 8.60	-2.56	<b>.03</b>	-0.55
Reaction time	0.71 $\pm$ .25	0.72 $\pm$ .26	-0.16	.88	-
Balance					
COP path length DS firm	15.53 $\pm$ 3.97	17.06 $\pm$ 8.81	-0.87	.41	-
COP path length SL firm	43.05 $\pm$ 11.25	40.52 $\pm$ 14.40	0.73	.48	-
COP path length TS firm	32.12 $\pm$ 17.62	34.16 $\pm$ 16.04	-0.74	.48	-
COP path length DS foam*	37.51 $\pm$ 13.79	27.44 $\pm$ 8.84	4.06	<b>.004</b>	0.87
COP path length SL foam*	59.97 $\pm$ 17.68	48.22 $\pm$ 17.78	3.80	<b>.005</b>	0.66
Length of COP TS foam	59.69 $\pm$ 24.03	45.81 $\pm$ 18.82	1.73	.12	-
Velocity of COP DS firm	0.78 $\pm$ .20	0.85 $\pm$ .44	-0.86	.41	-
Velocity of COP SL firm	2.15 $\pm$ .56	2.03 $\pm$ .72	0.73	.48	-
Velocity of COP TS firm	1.61 $\pm$ .88	1.71 $\pm$ .80	-0.74	.48	-
Velocity of COP DS foam*	1.88 $\pm$ .69	1.37 $\pm$ .44	4.06	<b>.004</b>	0.88
Velocity of COP SL foam*	3.00 $\pm$ .88	2.41 $\pm$ .89	3.80	<b>.005</b>	0.66
Velocity of COP TS foam	2.98 $\pm$ 1.20	2.29 $\pm$ .94	1.73	.12	-
Symptoms					
PCSS scores*	33.11 $\pm$ 23.17	18.00 $\pm$ 30.09	3.37	<b>.01</b>	0.56

\*Indicates statistical difference. Bold indicates statistical significance.

resting HR and BP. All HR and BP measurements, however, both pre- and post-treatment were within normal and healthy ranges. Gall (11) examined concussed individuals and reported no differences in HRV at rest when comparing concussed hockey players, with matched non-concussed controls (11). Conversely, exercise testing produced significant differences between the concussed and healthy controls (11). Furthermore, following traumatic brain injury normalization of the function between the autonomic and cardiovascular systems may take up to six months following injury (44). Given the mean number of 99.88 days for participants experiencing PCS in the current study, the normalization described may not have been completed. The lack of change in resting HR observed in the present pilot study in combination with other reported results within the literature by Gall et al. (11) and King et al. (44) warrant further study of HRV rather than resting HR in response to an AEB treatment program for individuals with PCS.

Unexpectedly, concentrations of salivary-BDNF did not significantly increase at the group level in response to the 12 session AEB treatment program. It was hypothesized that salivary-BDNF concentration levels might be low before beginning the AEB treatment, and that 12 sessions of aerobic exercise might result in an increase in salivary-BDNF concentrations. In a previous study, the implementation of a 12 session AEB program resulted in an increase in mean salivary-BDNF concentration levels from 548.98 pg/mL (pre-treatment) to 796.17 pg/mL (post-treatment) in a sample of 10 university aged, healthy, and physically active individuals (42). Increased salivary-BDNF levels in healthy and regularly physically active individuals provided a rationale for the implementation of AEB treatment for individuals with PCS. In this sample of participants with PCS, salivary-BDNF concentrations did not significantly change from pre-AEB treatment (226.01 pg/mL) to post-AEB treatment (209.33 pg/mL). Mean pre-treatment salivary-BDNF concentrations in the PCS group were less than half of what was reported in a healthy group. Furthermore, the mean post-treatment PCS group salivary-BDNF concentrations were nearly one quarter of the mean concentration levels reported in healthy individuals following an AEB treatment (42). The low salivary-BDNF concentration findings in this study for individuals with PCS are in agreement with the reported results regarding other neurodegenerative/neuropsychiatric conditions prior to administering an aerobic exercise program (32). Notwithstanding varying methodologies, previous studies that implemented aerobic exercise programs for Alzheimer's Disease, stroke, traumatic brain injury, and depression have cited notable improvements in symptoms and function (28,33,45–48). These observed improvements were attributed to improved BDNF concentrations. Exercise parameters including frequency, intensity, and length of treatment may account for the lack of increase in salivary-BDNF concentrations in this study. The intent of the AEB treatment program was to explore the feasibility of having participants complete 12 exercise sessions over the span of four weeks (three sessions per week, in approximately 28 days), while avoiding any symptom exacerbation. The results showed that the participant who completed the AEB program in the shortest amount

of time exhibited the largest salivary-BDNF concentration increase; whereas the participant who took the longest to complete the treatment had the smallest BDNF concentration change. These findings suggest that the frequency of sessions in a given period of time and the overall length of program could possibly have an influence on salivary-BDNF levels in individuals with PCS. Also, the intensity of exercise sessions may have been less than ideal to promote an increase in BDNF. Other neurological studies on aerobic exercise programs and BDNF concentrations recommended that moderate intensity exercise performed five to seven days per week should illicit an ideal BDNF response (28,45,46,48,49). Furthermore, acute bouts of high intensity stationary cycling or running have been reported to induce the greatest improvements in BDNF concentration in the short term in healthy individuals; and these improvements were related to improved learning and memory (21,50). Although, in the case of acute concussion and PCS, high intensity exercise may not be efficacious or indicated due to the risk of symptom exacerbation. The starting intensity of the aerobic component of the AEB program was extremely low (20% HRR), which was successful in regards to avoiding symptom exacerbation. Participants, however, did not reach moderate intensity exercise until sessions 10–12 in the AEB program, which may be responsible for the lack of BDNF changes observed in this study compared to a similar study on healthy individuals. Within the literature, it is well established that low BDNF levels are associated with neurological dysfunction, and this AEB treatment demonstrated positive effects on three of five individuals with PCS who had the lowest pre-treatment salivary-BDNF concentrations. The findings of this pilot study suggest that further research is necessary to determine the ideal frequency, intensity, and length of therapeutic aerobic exercise treatment necessary to increase BDNF concentrations in participants experiencing PCS. In addition, further investigation is needed to determine why the mean salivary-BDNF concentrations observed in this PCS sample were so much lower than concentrations seen in a sample of healthy subjects after completion of a similar AEB program (42). These salivary-BDNF concentration differences between healthy individuals and participants with PCS may be partially explained due to the fact that the healthy participants completed more exercise sessions at moderate intensity, and healthy participants averaged fewer days to complete the 12 exercise sessions than the PCS sample. Future studies should begin aerobic exercise at an initial intensity greater than 20% of HRR, as long as symptoms are not exacerbated. Additionally, a higher frequency and/or a longer duration of AEB treatment sessions may induce greater improvements in salivary-BDNF concentration levels. Avoiding symptom exacerbation, however, must always be the goal when administering aerobic exercise to individuals with PCS.

Investigations have revealed that normal neurophysiological processes of the brain are impaired as a result of acute concussion, and these impairments may continue to persist for individuals with PCS (7,9,14,51–53). Impaired neuroelectric connectivity has been reported in several other studies of PCS utilizing more sophisticated measures of cognitive function such as functional magnetic resonance imaging (fMRI) or

electroencephalography to assess event-related potentials during functional cognitive tasks (9,14,51–53). Leddy et al. (14) implemented an aerobic exercise based intervention to individuals with PCS and reported significant improvements in brain activation patterns during a math task when compared to participants with PCS receiving a placebo stretching treatment, and healthy non-concussed controls. In the current pilot study, the ImpACT battery was used to assess cognitive functions in response to the AEB treatment. No changes were observed in visual memory, verbal memory or reaction time, while a significant improvement in visual motor processing speed was detected. The ImpACT findings from the current pilot study replicate findings reported by Gagnon et al. (15), wherein visual motor processing speed was significantly improved following active rehabilitation for PCS, but all other cognitive variables were unchanged. The absence of verbal and visual memory improvements may be attributed to the variable BDNF concentration in response to treatment, wherein higher levels of BDNF are thought to facilitate improved performance on memory tasks. Therefore, the higher performance on visual motor speed observed within the current study may not be related to BDNF concentration levels. Exercise-induced increases in BDNF concentration levels have been reported to regulate mechanisms of neuroplasticity, which in turn facilitate improved hippocampal learning and memory (21,24,50). The small sample size in this pilot study and the variable inter-participant response in salivary-BDNF levels following treatment observed could explain the absence of statistically significant changes in verbal memory, visual memory and reaction time in response to the AEB treatment program. Improvements in cognitive function were expected based on literature reporting exercise-induced upregulation of BDNF concentrations and possible associated improvements in neuroplasticity. It is also possible that if the AEB treatment program sessions were administered more frequently, at a moderate intensity level, for longer than 12 sessions, higher salivary-BDNF concentration levels may have been observed. These higher concentrations may have facilitated greater improvements in verbal memory, visual memory and reaction time as measured by the ImpACT battery. Lack of significant changes in verbal memory, visual memory, and reaction time as measured by the ImpACT battery may also be explained by the variable nature of concussion. Severity of symptoms depends on a large number of factors including age, sex, the magnitude of impact, the area of the brain affected and history of previous concussions (6). Additionally, the underlying PCD(s) that may be causing persistent PCS symptoms need to be considered (8). Persistent concussion symptoms caused by physiologic PCD may exhibit a greater improvement in cognitive functions following AEB treatment due to improved glucose metabolism, and possible increases in BDNF concentrations. Vestibulo-ocular or cervicogenic PCDs may not demonstrate improved cognitive function following AEB treatment since the respective underlying mechanisms of each PCD would not be addressed.

The BESS protocol was utilized within this study as a standardized measure to assess balance for individuals following concussion (54,55). Significant reductions in velocity and

the length of COP path were observed in both DS and SL performed on a foam surface. These results suggest that the treatment program did have an effect on improving static balance for individuals suffering from PCS. Improved balance during DS on a foam surface may indicate greater control of balance during prolonged periods of standing at school, work, or during daily/sport-related activities. In a sporting context, improvements in SL balance on a firm surface may have the most clinical relevance. Sports such as ice hockey or rugby expose the athlete to many instances when he/she will have to maintain his/her balance on one leg dynamically and statically. Improved balance in SL on a foam surface may carry over to returning to play in sports that often demand the athlete to be able to control him/herself on one leg. Furthermore, better balance in an unstable position such as SL may lower re-injury risk by reducing the chance of a fall wherein another concussion may occur.

Exercise administered too soon following acute concussion has been documented to exacerbate symptoms and worsen outcomes of concussion (6,11,12). The significant reduction of PCSS scores observed within this pilot study concurs with the findings by other recent studies reporting exercise-based treatment improved PCS (14–16). These symptom improvements were observed in spite of the heterogeneous nature of how participants were initially concussed, in addition to the variable length of time they were experiencing PCS before starting the AEB treatment. Until the release of the newly updated Berlin Concussion Consensus Guidelines, the application of exercise as a treatment for PCS was mostly avoided as it was thought to worsen PCS due to evidence that exercise exacerbated symptoms of acute concussion and this same theory was applied to more persistent and chronic symptoms (6). Participants within this pilot study received rest-based treatment since he/she suffered the initial acute concussion that later developed into PCS. Persistent concussion symptoms continued to linger despite engaging in rest-based treatment. The most clinically relevant finding of this pilot study is that the tested AEB treatment elicited PCS improvements in symptom scores, as well as some associated benefits in regards to cognitive function and static balance. While this is consistent with other recent investigations, further investigation is required to reveal the underlying mechanisms of PCS that are affected and improved by exercise-based treatments. As evidence grows regarding PCDs more effective exercise-based treatment options can be developed in order to address these underlying factors of PCS.

A number of limitations were present in the pilot study and the interpretation of the results must take into consideration these limitations. First, a small pool of individuals with PCS was recruited for the current study. Second, there was not a large enough sample to recruit a control group of individuals with PCS, which may have an effect on the internal validity within the current study. Due to a small sample size, a delimitation of this study was that it was not possible to stratify participants with PCS into one of the three recently proposed PCD subgroups: physiologic, vestibulo-ocular, or cervicogenic (8). It is possible that individuals with a predominantly physiological cause for his/her PCS symptoms may benefit the most from an exercise program focused on

cardiovascular and balance retraining, via restoring normal physiological functions. Lastly, the ImPACT battery was used to assess cognitive functions before and after the AEB treatment program. The ImPACT is an affordable and widely used tool for assessing cognitive function; however, the ImPACT is predominantly intended to be used for establishing baseline cognitive performance in individuals who have not been concussed, and to assess the changes in cognitive function from baseline after an acute concussion. It is possible that changes in cognitive function may have occurred in response to the intervention but the ImPACT may have lacked the necessary sensitivity to detect these changes.

Future studies should investigate the administration of a similar supervised exercise program for individuals with PCS with a larger sample size, in order to allow for a control group as well as to stratify participants into physiological, vestibulo-ocular, and cervicogenic subgroups of PCS. More research is needed to determine the ideal frequency, intensity, time, and type of exercise that would be most effective at eliciting improvements in individuals with PCS. Future studies should also consider integrating alternative techniques to measure cognitive functions for individuals with PCS. Electroencephalography technology used to measure event-related potentials during cognitive tasks and/or fMRI during cognitive tasks may provide more information on the cognitive functions and communication within the brain while recovering from PCS.

## Conclusion

The findings of this pilot study suggest that the AEB treatment improved PCS reports using the PCSS, in addition to improvements in visual motor speed and in measures of static balance. Salivary-BDNF concentration levels were not significantly changed in response to the 12 session AEB program. Interestingly, the results from this pilot study suggest there may be an impairment in BDNF regulation for those with PCS, as PCS salivary-BDNF levels were lower than the levels observed in a sample of healthy subjects after the conclusion of a similar AEB treatment. Furthermore, the three participants with the lowest pre-treatment BDNF concentrations demonstrated the largest post-treatment effects on BDNF. Regardless, this may be due to a number of factors and warrants further investigation.

The preliminary evidence reported in the current pilot study is clinically relevant as our findings suggest exercise-based treatments may improve PCS outcomes in a more favourable manner than rest-based treatment. Moreover, the results of this study indicate that the AEB program is safe for people presenting with PCS, as study participants reported no adverse effects.

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## Declaration of interest

The authors report no declarations of interest.

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