Preconditioning cathodal transcranial direct current stimulation facilitates the neuroplastic effect of subsequent anodal transcranial direct current stimulation applied during cycling in young adults

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The study aimed to examine the effect of a pre-conditioning cathodal transcranial direct current stimulation (ctDCS) before subsequent anodal-tDCS (atDCS) was applied during low workload cycling exercise on the corticospinal responses in young healthy individuals. Eleven young subjects participated in two sessions receiving either conditioning ctDCS or sham stimulation, followed by atDCS while cycling (i.e. ctDCS-atDCS, sham-atDCS) at 1.2 times their body weight (84 ± 20 W) in a counterbalanced double-blind design. Corticospinal excitability was measured with motor evoked potentials (MEPs) elicited via transcranial magnetic stimulation with the intensity set to produce an MEP amplitude of 1 mV in a resting hand muscle at baseline (PRE), following pre-conditioning tDCS (POST − COND) and post atDCS combined with cycling exercise (POST-TEST). There was a significant interaction between time and intervention ($P < 0.01$) on MEPs. MEPs increased from PRE (1.0 ± 0.06 mV) to POST-TEST (1.3 ± 0.06 mV) during ctDCS-atDCS ($P < 0.001$) but did not change significantly across time during sham-atDCS ($P > 0.7$). Furthermore, MEPs were higher in ctDCS-atDCS compared to sham-atDCS (both $P < 0.01$) at POST − COND (ctDCS-atDCS: 1.1 ± 0.06 mV, sham-atDCS: 1.0 ± 0.06 mV) and POST-TEST (ctDCS-atDCS: 1.3 ± 0.06 mV, sham-atDCS: 1.0 ± 0.06 mV). These outcomes demonstrate that pre-conditioning cathodal tDCS can enhance subsequent corticospinal excitability changes induced by anodal tDCS applied in combination with cycling exercise. The findings have implications for the application of tDCS in combination with cycling exercise in rehabilitation and sporting contexts.

1. Introduction

It is relatively well established that regular participation in whole-body exercise (e.g. running, cycling) can have a positive impact on intrinsic brain network plasticity and connectivity [1,2]. These neurophysiological changes may also translate into functional behavioural improvements in cognitive and motor performance [3,4]. Despite these findings, studies probing the influence of cycling exercise on corticospinal excitability provide mixed outcomes. For example, low intensity cycling exercise does not modulate net corticospinal tract excitability but attenuates intracortical inhibition when measured in a non-exercised muscle [5–7]. It is speculated that the attenuation in intracortical inhibition likely contributes to the creation of a cortical environment that is optimal for plasticity, via increased levels of brain derived neurotrophic factor (BDNF) [8]. However, the lack of a change in corticospinal excitability makes this interpretation difficult. It is possible that the effect of cycling exercise on corticospinal excitably represents a homeostatic metaplastic mechanism [9], although, this remains elusive.

Non-invasive brain stimulation (NIBS) is known to induce neuroplastic changes in the brain. These modifications are manifested in either long-term potentiation (LTP) or long-term depression (LTD) of synapses [10]. Transcranial direct current stimulation (tDCS) is an emerging NIBS technique which can be used to deliver weak electrical currents to the brain in order to modulate the excitability of the primary motor cortex (M1) in humans [10]. Cathodal tDCS (i.e. ctDCS; cathode placed over M1) may produce LTD-like effects while anodal tDCS (i.e. atDCS; anode placed over M1) may elicit LTP-like effects [11]. A few

Abbreviations: TMS, transcranial magnetic stimulation; MEPs, motor evoked potentials; atDCS, anodal transcranial direct current stimulation; ctDCS, cathodal transcranial direct current stimulation; M1, motor cortex; EMG, electromyography; FDI, first dorsal interosseous; RMT, resting motor threshold; NIBS, non-invasive brain stimulation

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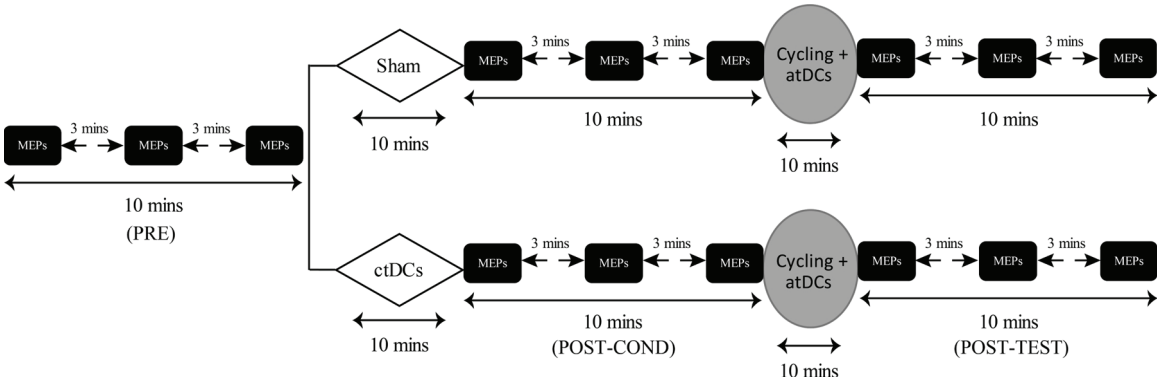

Fig. 1. Schematic of experimental protocol. Resting motor threshold and stimulus intensity to evoke a 1 mV response was measured at the start of the experimental session (not shown in figure). A set of MEPs (i.e. 3 blocks of 15 transcranial magnetic stimulations) was collected in both sessions as baseline (PRE) prior to conditioning (COND) tDCS. Subjects were given a conditioning dose of either ctDCS (10 min at 2 mA) or sham (30 s stimulation + 9.5 min no stimulation) immediately after PRE. MEP measurements were repeated immediately after conditioning tDCS (POST − COND) and atDCS combined with cycling exercise (POST-TEST).

recent studies have demonstrated the effectiveness of atDCS in modulating corticospinal excitability and motor performance [12–15]. However, the outcomes in relation to its efficacy are variable, likely represented via differences in experimental manipulations, such as site, intensity and duration of stimulation, as well as inter and intra-individual variability [16–19].

There is increasing evidence to demonstrate that pre-conditioning the brain by reducing the activation threshold of the neurons can facilitate the effect of subsequent stimulation inducing larger LTP-like effects [20–22]. A possible mechanism to explain the enhancing effect of pre-conditioning stimulation is homeostatic metaplasticity [23], which proposes that synaptic plasticity is bidirectional and previous level of synaptic activity may alter the response to the subsequent NIBS. Essentially, higher post synaptic activity will increase the synaptic modification threshold, while lower post synaptic activity will decrease the threshold and facilitate the induction of LTP-like effects [23]. In agreement with this proposition, studies using tDCS have demonstrated that pre-conditioning cathodal tDCS can amplify the effect of subsequent anodal tDCS to increase corticospinal excitability and improve motor skill performance [24,25]. For instance, when cathodal tDCS precedes anodal tDCS, completion time of a grooved pegboard test is significantly reduced compared to shamtDCS – atDCS and shamtDCS – shamtDCS conditions [24].

The aim of the current study was to investigate the effects of pre-conditioning ctDCS on corticospinal excitability tested with transcranial magnetic stimulation (TMS) evoked potential (MEP) after low intensity cycling exercise performed with concurrent atDCS in young healthy individuals. We hypothesised that, pre-conditioning ctDCS (but not pre-conditioning sham) will enhance the LTP-like effects of the subsequent atDCS combined with a low intensity cycling exercise to facilitate corticospinal excitability.

2. Methods

2.1. Subjects

Eleven young (20.9 ± 0.2 years; 4 females) healthy subjects (height: 172 ± 2 cm; weight: 71 ± 3 kg) were recruited through advertisement in the university. All subjects were right handed (handedness laterality index: 0.86 ± 0.02) in accordance with the Edinburgh Handedness Inventory [26]. Participants with contraindications to TMS or tDCS including a history of epilepsy, stroke, neurological illness, or those who were consuming psychoactive medications at the time of the study were excluded from participation. Each subject gave their written informed consent prior to participation and was instructed to avoid any strenuous activity at least 24 h prior to the experimental sessions. The study was approved by the University of Adelaide Human Research Ethics Committee and conducted in accordance with the Declaration of Helsinki.

2.2. Experimental protocol

Subjects were set-up on the cycle ergometer with their feet strapped into the pedals and their hands placed on the handlebars. Subjects were asked to minimise the motion of their right wrist, forearm and hand throughout the experiment. There were two experimental sessions, and each session was separated by a week. In addition, both sessions were conducted between 2 pm to 5 pm and repeat sessions were conducted at the same time of the day to minimise the confounding influence of diurnal variations in cortisol on cortical plasticity [27].

During the two sessions, subjects received a dose of pre-conditioning tDCS of either sham or ctDCS in a counter-balanced, double-blinded approach. Subjects then performed a low intensity cycling exercise on a mechanically braked cycle ergometer (Velotron, Elite Model, Racer Mate, Seattle, WA) for 10 min (power output of the cycle ergometer was set at 120 percent of participant's body weight; group mean workload = 85 ± 3 W; and 80 rpm fixed cadence) while atDCS was applied over the M1 area concurrently (see Fig. 1). The rationale for implementing this cycling intensity (i.e. < 100 W) was to allow the participants to perform the exercise relative to their body weight so that the development of fatigue could be avoided –an occurrence that can independently influence corticospinal tract excitability [28,29].

MEPs (i.e. 3 blocks of 15 TMS) were collected over a 10 min period at three time points; baseline, immediately post pre-conditioning stimulation and immediately post atDCS combined with cycling exercise (i.e. PRE, POST − COND and POST-TEST respectively) (Fig. 1).

2.3. Experimental procedures

2.3.1. Electromyography recordings

After skin preparation with abrasion and alcohol swabs, surface electrodes were positioned over the muscle belly and tendon of the right first dorsal interosseous (FDI). EMG was recorded via a monopolar configuration (Ag-AgCl, 10 mm diameter, inter-electrode distance: 2.9 ± 0.1 cm). EMG signals were amplified (100–1000 times; MA300 DTU, Motion Lab Systems, USA), band pass filtered (30–1000 Hz) and analogue to digitally converted at a sampling rate of 2000 Hz using a 16-bit power 1401 and Signal 4.11 data collection software (Cambridge Electronic Design, UK) via custom written scripts. Collected data was stored on a laboratory PC for offline analysis.

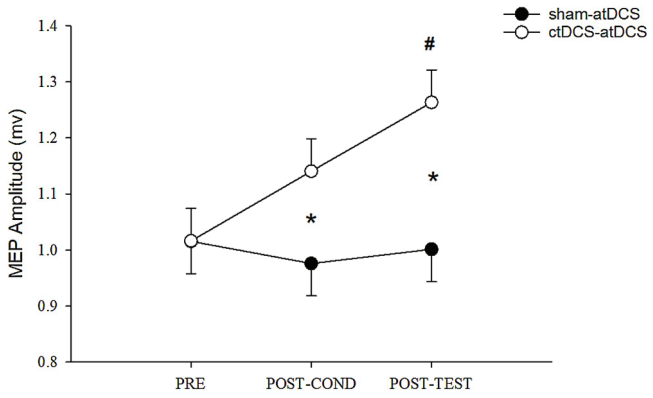

Fig. 2. Corticospinal excitability (i.e. MEP amplitude) at baseline (PRE), after ctDCS or sham conditioning (POST − COND) and after cycling exercise performed with atDCS (POST-TEST) in the two sessions. Data are expressed as the MEP amplitude (mean ± SE). $^{*}P < 0.05$ between sessions; $^{\#}P < 0.05$ from PRE in ctDCS - atDCS session.

2.3.2. Transcranial magnetic stimulation (TMS)

Single-pulse TMS was delivered to the left M1 using a MagStim 200 (monophasic) magnetic stimulator (MagStim, Dyfed, UK) and a figure-of-eight coil. The coil was placed tangentially to the scalp with an angle of approximately 45° posteriorly producing a current flow within the motor cortex in the posterior-anterior direction. The optimal location that gave the largest MEP at a fixed stimulation intensity in the resting FDI hand muscle was marked directly on the scalp to ensure consistent positioning of the coil. Resting motor threshold (RMT) was defined as the minimum stimulator intensity (MSO) which produced an MEP amplitude of at least 50μv in 5 out of 10 successive stimulations [30] was determined to ensure that the effective TMS intensity set to produce an MEP peak-to-peak amplitude of 1 mV in the resting FDI [30] was consistent across sessions.

2.3.3. Transcranial direct current stimulation

tDCS was delivered through a direct current electrical stimulator (NeuroConn DC-Stimulator, Germany) connected to a pair of saline soaked electrodes (25 cm^2). For ctDCS, the cathode was placed over the left motor cortex corresponding to the FDI representation (determined via mapping with TMS – see 'TMS' above) with anode on the right supraorbital area and for atDCS, the placement of the electrodes was reversed [31]. Stimulation was applied at an intensity of 2 mA for a period of 10 min (atDCS, ctDCS) or 30 s followed by 9.5 min. of no stimulation (sham) [19]. In order to minimise the discomfort caused by electrical transients, 10 s of fade in and fade out current was set at the start and end of the stimulation period [10]. The selection of pre-conditioning tDCS (either ctDCS or sham) and test tDCS (atDCS) in each of the two experimental sessions was double blinded to both the subject and the main experimenter. At the end of each tDCS dose, subjects were asked to report the sensations associated with the stimulation. It was clear from the subjects' subjective responses that the type of stimulation received was not discernible and subjects mainly felt slight tingling at the site of the electrode [32].

2.4. Data analysis

Signal 4.11 software was used for offline analysis of the EMG data. Since the aim was to quantify corticospinal excitability (CSE) in a resting FDI muscle, in trials where muscle activity (measured as peak to peak EMG) was more than 20 μV in the 100 ms prior to stimulation, the data was removed from the analysis (< 1% of trials). MEP amplitude was measured as peak-to-peak amplitude and expressed in mV. MEP values were averaged across the three blocks of 15 TMS (i.e. 45 TMS) for each of PRE, POST − CONDITIONING and POST-TEST time points.

2.5. Statistical analysis

Normality of the data was confirmed by a Shapiro-Wilk W test. Paired t-tests were used to compare RMT and MEP amplitude across sessions (i.e. sham-atDCS; ctDCS-atDCS). Linear mixed model analyses with repeated measures were used to investigate the effect of time (i.e. PRE, POST − CONDITIONING and POST-TEST) and intervention (i.e. sham-atDCS, ctDCS-atDCS) on MEP amplitude. For linear mixed model analyses, subjects were included as random effect, and significant main effects and interactions were further investigated using custom contrasts with Bonferroni correction. Cohen's effect sizes (d_z) were calculated with G * Power software. Data (in text and figures) are presented as mean ± standard error of the mean. Statistical significance is set at $P < 0.05$.

3. Results

All participants completed the study with no adverse reaction. There was no statistical difference in RMT (41.9 ± 0.7% MSO for sham-atDCS and 40.9 ± 0.9% MSO for ctDCS-atDCS) and S_{1mv} (53.3 ± 1.4% MSO for sham-atDCS and 51.1 ± 1.4% MSO for ctDCS-atDCS) between interventions ($t_{20} < 0.64$; $P > 0.30$, $d_Z < 0.13$).

MEP amplitude (Fig. 2) differed significantly as a function of time ($F_{2,\ 774} = 4.7$, $P < 0.01$; $d_Z = 0.95$) and intervention ($F_{1,\ 303} = 21.1$, $P < 0.001$; $d_Z = 1.45$). In addition, there was a significant interaction between factors ($F_{2,\ 787} = 5.9$, $P < 0.01$; $d_Z = 1.75$). The increase in MEP amplitude was not statistically significant from PRE to POST − CONDITIONING ($P = 0.07$, $d_Z = 1.08$) in ctDCS-atDCS session, however, it significantly increased from PRE to POST-TEST ($P < 0.001$, $d_Z = 2.13$) in ctDCS-atDCS session. While MEP amplitude did not modulate across time in sham-atDCS session ($P > 0.9$, $d_Z < 0.28$), it was significantly lower in sham-atDCS session compared to ctDCS-atDCS session at both POST − CONDITIONING and POST-TEST time points ($P < 0.01$, $d_Z > 1.42$). Fig. 3 shows individual subject MEP response to neuromodulation across the two sessions.

4. Discussion

The present study aimed to investigate whether the efficacy of anodal tDCS applied during low workload cycling exercise over M1 to modulate corticospinal excitability will be altered when conditioned by cathodal tDCS applied over M1. The main outcome of the study was that pre-conditioning cathodal tDCS facilitated corticospinal tract excitability following anodal tDCS applied in combination with cycling exercise. Specifically, MEPs increased (by approximately 13%–117% in the 8 out of 11 participants in whom an increase was evident) compared to baseline when anodal tDCS applied during cycling exercise was primed with cathodal tDCS. Since this increase was not evident when anodal tDCS applied during cycling exercise was primed with sham, the outcomes suggest that pre-conditioning ctDCS may potentially be used as a tool to improve the neuroplastic response to cycling exercise and consequently motor function.

4.1. tDCS mediated effect on the neuroplastic response to cycling exercise

There is increasing evidence that locomotor exercise create a cortical environment that is optimal for neuroplasticity [33,34], and may consequently have a positive influence on brain structure and functions, including memory and motor skill learning [3,35]. The underlying neurophysiological mechanisms of the neuroplastic response to locomotor cycling remain elusive, although animal work suggest that increased levels of brain derived neurotrophic factor (BDNF) may contribute [8]. Interestingly, even though human studies using non-invasive brain stimulation techniques suggest that a short bout of cycling exercise attenuates the magnitude of $GABA_A$ – mediated inhibition [5,6], these studies have shown no change in corticospinal excitability

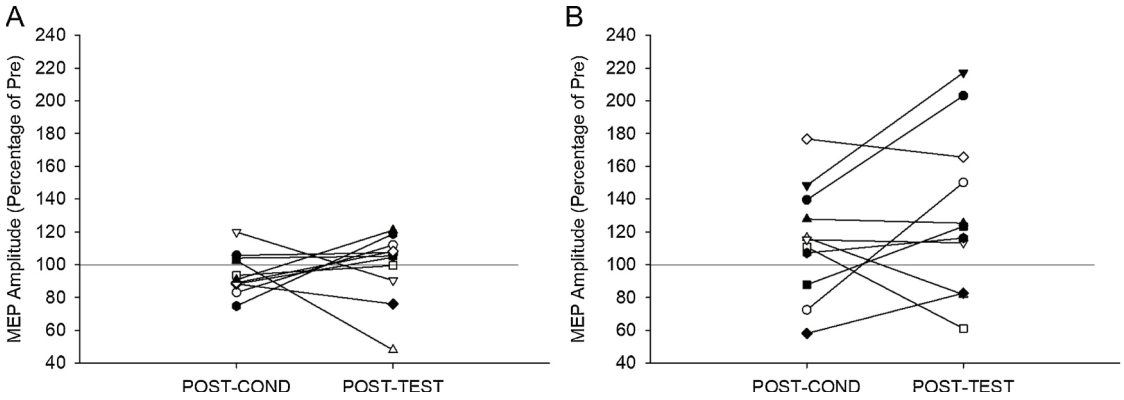

Fig. 3. Scatter plot of individual subject MEP (expressed as percentage of Pre) at Post-conditioning (POST − COND) and Post-test (POST-TEST) during sham-atDCS session (A) and ctDCS-atDCS session (B).

measured with a TMS-evoked MEP response [5–7]. The factors associated with the lack of a change in the corticospinal tract excitability post cycling exercise remain unknown. However, it is well-understood that the induction of neuroplastic response in healthy humans is influenced by many factors, including the history of activity within the targeted neuronal network [36,37] which is thought to be particularly important. For example, synaptic potentiation is dampened following high neuronal activity (e.g. repetitive locomotor movements such as walking and cycling that are known to increase cortical excitability [38,39]), but increased following low neural activity [40,41]; an effect that represents homeostatic metaplasticity to maintain network integrity [40]. Therefore, it is possible that the lack of a neuroplastic response (i.e. no change in an MEP) reported post single bout of cycling exercise in previous work [5–7] is in accordance with Bienenstock-Cooper-Munro theory of homeostatic metaplasticity [23]. The findings of our study support this notion. We used tDCS to induce activity-dependent plasticity (i.e. long-term depression; LTD and long-term potentiation; LTP) at pre-and-during low workload cycling exercise and show a homeostatic metaplastic response in the individuals studied. This experimental design is prudent since contrary to other forms of neuromodulation (e.g. paired associative stimulation and repetitive TMS [42,43]), tDCS can be applied simultaneously with motor activity to influence corticospinal excitability and promote function [44,45]. Specifically, MEPs were facilitated when ctDCS (which is expected to induce LTD-like effect by decreasing the neuronal activity to reduce the threshold for subsequent stimulations that increase excitability of neurons [20]) was used to condition the atDCS applied during cycling exercise. This effect was not apparent when pre-conditioning sham stimulation was applied. The outcomes of this study provide evidence to demonstrate that pre-conditioning ctDCS may be necessary to induce LTP-like plasticity with atDCS during cycling exercise. One important consideration in the current study is the high degree of variability i.e. 13%–117% potentiation in 8 out of 11 participants in the ctDCS-atDCS session. The after-effects of NIBS have in fact been shown to be variable between and within participants, in terms of magnitude, duration and direction [46]. There are a multitude of factors that may contribute to NIBS response variability, including physical activity levels, attention, sex and optimal stimulation dose [46–48]. The findings of this study support the issue of variability associated with NIBS within the broader field [19,48] and further highlights the need for more research to determine the individual factors that influence responsiveness to NIBS and to develop more effective stimulation paradigms that would augment replicability of findings.

The effect with ctDCS over M1 observed in the current study (i.e. no significant change – but tendency for an increase) is consistent with recent findings where no change [25] or even an increase [9] was evident after 10–20 minutes of pre-conditioning ctDCS. The variability in the response to ctDCS may partly be explained by the fact that about 50% of the population have poor or absent responses to tDCS [19]. It is also important to note that pre-conditioning stimulation can still be effective at inducing metaplasticity even without modulation of synaptic efficacy [40] or an overt modulation of MEP amplitude [30,45,49,50]. For example, conditioning with NIBS that is expected to induce LTP or LTD may not alter MEPs as standalone, but can have an opposing effect on subsequent NIBS response [30,49,51]. In the current study, if anything, we show a tendency for an increase in MEPs after ctDCS. While the underlying mechanism for this effect is not clear, it is possible that such a ctDCS mediated 'increase' (in non-responders) is important to facilitate the effects of subsequent atDCS. However, this possibility remains speculative.

4.2. Methodological considerations

There are several limitations in the present study. First, we did not measure corticospinal excitability after cycling exercise without the application of tDCS. However, the lack of a modulation in corticospinal excitability post normal cycling exercise has been documented in numerous previous studies in both exercised and non-exercised muscles [5–7]; and the fact that we did not observe any change post shamtDCS-atDCS session suggests that it is unlikely a change would have been observed after cycling (without concurrent atDCS). In any case, the objective of the study was to establish an optimal tDCS pre-conditioning paradigm applied during cycling that would facilitate corticospinal excitability. Another consideration is the fact that the development of homeostatic metaplasticity is dependent on the timing between pre-conditioning and subsequent neuromodulatory stimulation, whereby a longer interval of 30-min has recently been indicated to be most effective [30,52]. While the pre-conditioning and test neuromodulation were separated by 10 min in the current study, future studies should probe the effect of time between pre-conditioning tDCS and atDCS applied during cycling exercise on the activity-dependant metaplastic response. The small sample size of this study should be acknowledged; although, it should also be noted that the effect sizes were considered relatively large ($d_z > 0.8$). The physical activity levels of participants was not measured and this may have influenced the induction of cortical plasticity [34]. Finally, the influence of corticospinal potentiation on behavioural outcomes (e.g. motor skills, cognitive function, exercise tolerance) and the relationship of this potentiation with $GABA_A$ and $GABA_B$ mediated inhibition [24,25] remains unknown. These aspects will form an important extension of the current study.

4.3. Conclusion & significance

In conclusion, the study provides evidence to show that ctDCS pre-conditioning can improve the neuroplastic response (demonstrated with increased corticospinal excitability) to atDCS applied during low

workload cycling exercise. Importantly, the findings of this study suggest that the typical lack of an increase in corticospinal response (known to represent activity-dependent neuroplasticity) seen post cycling exercise may be facilitated with external stimuli (i.e. tDCS); and in particular, pre-conditioning ctDCS optimizes the corticospinal tract for upcoming combined effect of cycling and atDCS. These preliminary findings are of significance and have the potential to contribute to the development of tDCS pre-conditioning protocols that may be used in sporting, clinical, rehabilitation and defence settings involving locomotor whole body movements to improve functional motor and cognitive function.

Author contributions

SS conceived and designed the study. MP and SS executed the study. MP and SS analysed data. MP and SS prepared figures and initial draft of the manuscript. SS and BL interpreted the data. All authors contributed to writing and approved the final version of the manuscript.

Declaration of competing interest

The authors declare no conflict of interest

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