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Effects of Movement-Based and Cognitive Priming on Brain Function

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Abstract

Introduction: Priming involves exposure to a stimulus in order to elicit a behavior change related to motor learning. Priming may involve neurostimulation, pharmacology, exercise, and mental imagery. The purpose of priming is to potentiate the effects of a subsequent activity. Past work demonstrated enhanced motor learning with the addition of a bout of priming delivered prior to a motor-learning activity. Despite these encouraging findings, limited work has investigated the effects of priming on brain function.

Purpose: To determine the effects of priming on brain function. This study focused on two modes of priming: aerobic exercise (movement-based) and cognitive (action observation).

Methods: Healthy, right-handed individuals (≥ 18 years) completed baseline testing consisting of a behavioral battery and a three-minute resting-state EEG recording. Participants were randomized to receive either a 5-minute movement- or cognitive-based priming intervention before crossing-over after 1 week to receive the remaining priming intervention. During these visits, participants completed a three-minute resting-state EEG recording before and immediately after priming. Movement-based priming consisted of walking on a treadmill while maintaining an established target heart rate range. Cognitive priming involved watching a video of individuals walking on a treadmill. Brain function was assessed by computing measures of [1] EEG power in leads overlying left (dominant) primary motor cortex (IM1), left dorsal premotor cortex (IPMd), and total power across the whole brain also by measuring [2] coherence (connectivity) between IM1 and rM1, IPMd, and the entire brain across the high beta (20-30 Hz) frequency band. Effects of priming on brain function were determined with paired t-tests.

Results: Data from nine individuals (seven females) aged 24 ± 2.8 years was included in the results. A significant increase in high beta coherence between electrodes overlying IM1 and

SMA ($t=3.08$, $p=0.018$) was observed following aerobic priming. No other significant findings related to any other motor-related areas were observed with either action observation or aerobic priming.

Conclusion: Across a 20-30 Hz frequency spectrum, a brief bout of priming effects brain function in a mode-dependent manner favoring aerobic priming.

Introduction

Priming is a form of implicit learning¹ that produces short-term changes in underlying neural synapses.² These synaptic modifications last long enough to alter the effects of an ensuing event which can be used to promote positive neuroplastic changes.² Taken together, we define priming as a session of neural conditioning delivered strategically to augment subsequent learning.³ There are several forms of priming, including the administration of non-invasive brain stimulation, pharmacology, cognitive training, and movement.^{1,4-6} Previous work has shown enhancement of motor learning in adults when priming precedes a motor-related task.^{4,7} The potentiation of motor learning induced by neural priming has clinical implications for individuals with motor deficits resulting from injury or disease, such as stroke, where motor re-learning represents an important goal in recovery and rehabilitation. Translating the potential benefits of priming from the laboratory to the clinic is an important next step.

Movement- and cognitive-based priming are clinically feasible priming strategies as therapists can immediately implement them into their existing plans of care. Several examples of movement-based priming exist and include bilateral motor priming involving symmetrical movements of both upper or lower extremities,^{5,8,9} unilateral priming involving voluntary movement of the affected extremity,⁹ and aerobic priming.⁴ In the latter, moderate intensity running, defined as achieving 65-85% of age-predicted maximum heart rate, led to improved accuracy in a novel upper extremity task in adults.⁴ Aerobic exercise priming in individuals with stroke has shown similar benefit as demonstrated by improved speed during a standardized upper extremity reaching task.¹⁰ Additionally, cognitive-based priming, entailing motor imagery (stationary guided visualization of a specific task or performance) and action observation (stationary viewing of a specific movement or performance of a specific task) also potentiates learning effects in both unimpaired individuals⁷ and those with stroke.^{6,11-15}

Despite encouraging evidence supporting the role of priming in potentiating motor learning in across various populations, the factors mediating the effects of priming remain unclear. Gaining an understanding of these underlying mechanisms will lead the optimization of priming delivery, including the timing between priming and a subsequent motor learning task, and the ability to delineate priming “responders” from “non-responders” which would improve the efficiency of clinical care. Previous work employing non-invasive brain stimulation¹⁶⁻¹⁹ and pharmacology²⁰⁻²² suggest that priming alters corticospinal excitability by means of substrates involved in long-term potentiation and depression.²³ Relatedly, movement-based priming, specifically aerobic exercise, has been shown to enhance the expression of brain-derived neurotrophic factor, a key substrate in motor learning²⁴ while also increasing corticospinal excitability.^{4,25,26} Additionally, research examining action observation purports similar neural network involvement as performing an action.²⁷ Relatedly, additional work shows that action observation activates the primary motor cortex that subsequently contributes to enhanced learning in both healthy individuals²⁸ and those with stroke.¹³ Collectively, these studies provide preliminary evidence that priming contributes to changes in motor behavior through alterations in neurophysiological function involving motor-specific structures. Obtaining a more specific understanding of neurophysiological function following priming is an important next step.

Electroencephalography (EEG) is an appealing neuroimaging approach to elucidating the neural mechanisms underlying priming given its portability and wide accessibility amongst individuals. EEG directly records electrical potentials from the brain.²⁹ Neuronal oscillations generated by these membrane potentials mediate behavioral and mental processes including movement and consciousness.^{30,31} Thus, neurophysiological measurements derived from neuronal oscillations may provide additional insight priming. EEG power and coherence are two examples. The former represents the magnitude of electrical activity in a defined frequency band and the latter is a surrogate measure of functional connectivity between two distinct brain regions based on consistent differences in signal amplitude and phase across time.^{32,33} Past work has shown that changes in EEG coherence, specifically in the high beta frequency band (20-30 Hz) in electrodes overlying motor and motor-related cortical regions are associated with motor learning and recovery post-stroke.^{34,35}

The purpose of this study was to examine potential changes in brain function following motor- and cognitive-based priming in healthy individuals using EEG. We hypothesize that priming with either aerobic exercise or action observations will elicit changes in brain function as measured

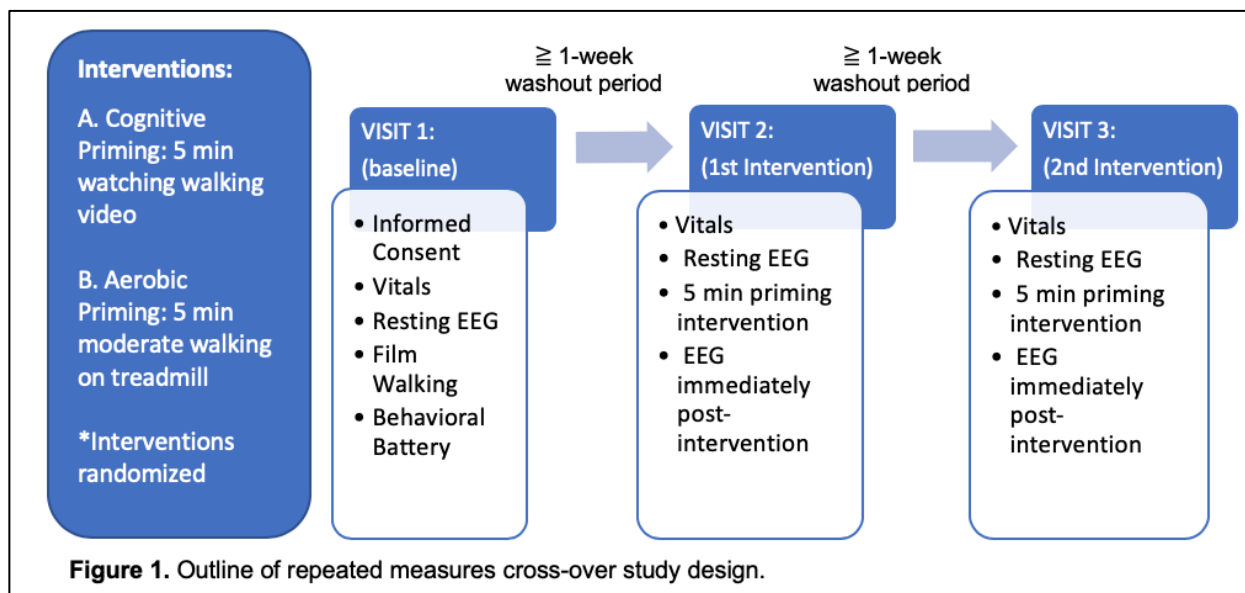
by increases in EEG power and coherence in motor-specific brain regions in the high beta frequency range.

Methods

Subjects

We recruited students at the University of North Carolina at Chapel Hill between the ages of 18 and 30 years old through email listservs. Additional inclusion criteria included right handedness, no history of cardiovascular or neurological conditions, and the ability to tolerate five minutes of moderate aerobic activity. Individuals were excluded from study participation if they had a resting blood pressure (BP) $\geq 180/110$ mmHg or cognitive impairment as defined by a Mini-Mental State Examination score < 24 . All subjects provided written informed consent as approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Subject participation involved three visits consisting of one baseline and two intervention visits as part of a repeated measures cross-over design study (Figure 1) with a one-week minimum washout period. Subjects were randomized to the order of priming interventions (described below). Prior to each visit, subjects received instruction to avoid caffeine and exercise occurring less than one hour prior to each study visit. If subjects were prescribed medication for depression, anxiety, or attention deficit hyperactivity disorder (ADHD), they were encouraged to take their medication at the same time each day during study participation.



Baseline Visit

During the baseline visit, subjects completed a medical history questionnaire and a behavioral battery consisting of the following tests: [1] Activities-Specific Balance Confidence Scale (ABC)³⁶, a 16-item self-report measure used to assess a participants' confidence in their balance while performing different activities, [2] General Practice Physical Activity Questionnaire (GPPAQ)³⁷, a self-report to assess individual physical activity level, [3] Beck Depression Inventory (BDI)³⁸, [4] Trail Making Test B³⁹ to assess executive function and visual attention, [5] Montreal Cognitive Assessment (MoCA)⁴⁰ to assess cognition, [6] 10-meter walk test to assess gait speed, [7] Mini Balance Evaluation System Test (BESTest test)⁴¹ to examine sensory orientation, postural responses, and gait stability, and [8] Nine-Hole Peg test⁴² to assess upper extremity function. Subjects also completed a three-minute resting-state EEG recording (described in detail below) followed by a video recording that entailed walking at a self-selected speed on a treadmill. Video recordings of treadmill walking included one-minute long clips of frontal, lateral, and posterior views.

Intervention Visits

At the start of each intervention visit, investigators collected subjects' resting vitals (heart rate and blood pressure). Subjects then completed a three-minute resting-state EEG recording followed by one five-minute bout of either aerobic (movement-based) or cognitive (action observation) priming. Immediately after priming, subjects completed an additional three-minute resting-state EEG recording followed by additional EEG recordings at 10, 20, and 30 minutes post-priming. The focus of this report is the immediate (pre to post) change in EEG measures of power and coherence following priming.

Aerobic Priming

Participants were given a target heart rate (HR) zone (Target HR Lower Limit = $[0.6 \times (\text{Max HR} - \text{Resting HR})] + \text{Resting HR}$) (Target HR Upper Limit = $[0.8 \times (\text{Max HR} - \text{Resting HR})] + \text{Resting HR}$) and asked to walk at a moderate intensity for five minutes while maintaining their HR in the aforementioned zone. HR and oxygen saturation were measured continuously for the duration of the walking activity. Participants were instructed to increase only the speed of the treadmill, maintaining a brisk walk at their target HR for five minutes. To assess physiologic response and ensure adequate HR elevation, vitals were monitored for the five minutes, and values for HR and oxygen saturation were recorded on one-minute intervals. During treadmill walking, subjects did not receive any visual feedback and physical support with the exception of intermittingly holding onto the treadmill bar during pulse oximetry.

Cognitive Priming

Participants were instructed to sit upright in a chair two to three feet from a computer monitor to view a five-minute long video. The video contained 15-second clips of healthy individuals walking on a treadmill at a self-selected pace from posterior and lateral viewpoints. The video also included five randomly inserted clips of the participant walking on the treadmill (previously recorded during the baseline visit). To ensure consistent attention throughout the duration of the video, participants were instructed to count the number of clips they saw of themselves walking.

EEG Acquisition

EEG data was acquired using a dense-array 256-lead system (Figure 2, Philips Electrical Geodesics, Inc., Eugene, OR). During the three-minute recording, the EEG signal was referenced to electrode Cz and referenced to the average of all leads for subsequent analyses. Subjects maintained a seated position and received instruction to remain still and avoid talking. Subjects focused on a central fixation cross projected on a computer screen located approximately two feet from the subject. EEG data was collected at 1000 Hz using a high input impedance Net Amp 400 amplifier and Net Station 4.5 software (Philips Electrical Geodesics Inc., Eugene, OR).

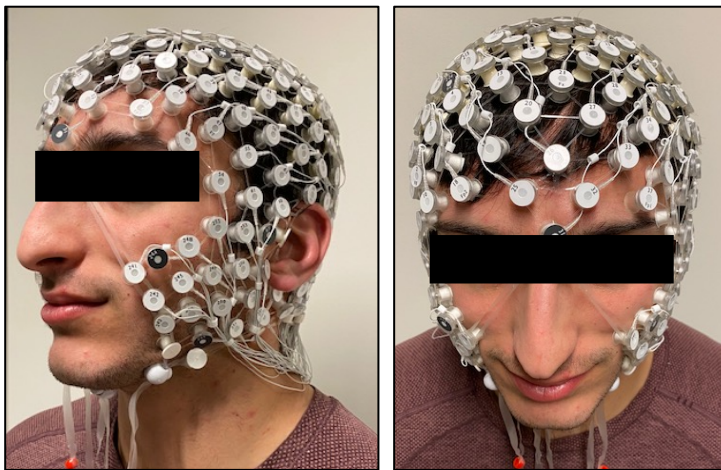


Figure 2. High dense-array electroencephalography cap consisting of 256 leads.

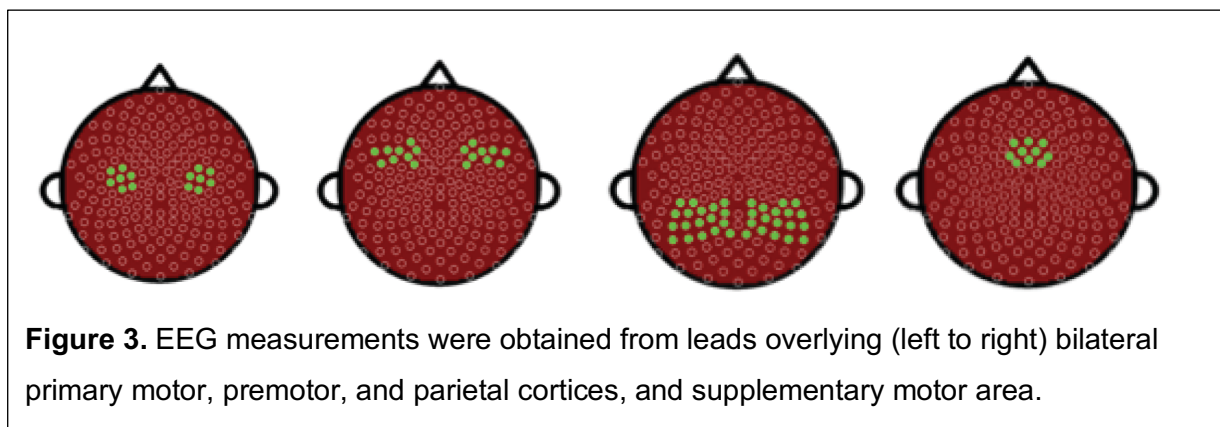
EEG Preprocessing

Raw and unfiltered EEG data was transferred to Matlab (R2017b, MathWorks, Natick, MA) for offline preprocessing using EEGLAB⁴³ version 2019.0. EEG data was low-pass filtered at 40 Hz,

high-pass filtered at 0.5 Hz, and segmented into one-second non-overlapping epochs. Data was visually inspected, and epochs demonstrated muscle activity were removed. Next, data underwent an Independent Component Analysis (ICA) decomposition. Based on the frequency spectra, component activity, and amplitude topography maps, components showing non-brain features, e.g. eye blinks, eye movement, channel and line noise, and muscle and cardiac activity were removed. Following the ICA component classification, data was visually inspected one last time to remove epochs showing blink artifact. Clean data then underwent a surface Laplacian transformation to mitigate volume conduction effects.⁴⁴

EEG Coherence and Power

EEG measures of coherence and power were obtained from the preprocessed data across a 1-30 Hz frequency band. Coherence is a measure of functional connectivity between EEG signals.⁴⁵ Values are reported as the analogue of the squared correlation coefficient and range from 0 (indicative of random amplitude ratios and phase differences between signals across time) to 1 (indicating consistent amplitude ratios and phase differences ratios across time). We examined interhemispheric connectivity between electrodes overlying left and right primary motor cortices (IM1, rM1) and intrahemispheric connectivity using IM1 and rM1 as seed regions (defined as electrodes C3 and C4 and the surrounding six leads, respectively) and computing coherence between these seed regions and a predefined motor network consisting of supplementary motor (SMA), dorsal premotor (PMd), and parietal (Pr) cortices. Figure 3 illustrates these electrode groups.



A spectral analysis was performed by submitting the EEG time series to a discrete Fast Fourier transform. Relative power was calculated by dividing power in a given frequency band for each electrode by the total power summed over the 1-30 Hz range. We computed power

measurements from leads overlying bilateral M1, PMd, Pr, and SMA. Our primary frequency band of interest for measures of coherence and power was high beta (20-30 Hz) given the role of high beta oscillations in motor system function.^{34,35}

Statistics and Data Analysis

All statistical procedures were performed with JMP software (version 14.0, SAS Institute Inc., Cary, NC). Parametric statistical methods were used for all data that was either normally distributed or transformed to achieve a normal distribution as indicated by the Shapiro-Wilk W test; else, nonparametric methods were used. To determine if significant changes in EEG measures (power and coherence) occurred immediately following movement- and cognitive-based priming, we computed two-sided paired t-tests. Due to the exploratory nature of this study and limited sample size, we did not correct for multiple comparisons. An alpha value of 0.05 denoted significance.

Results

Subjects

We enrolled a total of 18 individuals with 17 completing all study visits. Due to EEG noise from excessive movement artifact and line noise, the quality of the data prohibited further analysis resulting in usable data from nine individuals for movement-based (n=8) and cognitive-based (n=7) priming. Of the nine included subjects, three were taking medications related to anxiety (n=2) and ADHD (n=2). Six participants self-reported a physically active lifestyle according to the General Practice Physical Activity Questionnaire (GPPAQ), while moderately active or an inactive lifestyle were each reported by one participant. on the GPPAQ. Table 1 provides a summary of additional participant data. Subjects did not experience nor report any adverse events following movement- and cognitive-based priming sessions.

Table 1. Subject Demographics and Clinical Assessment Scores

	Sex	Age (years)	Hand	Vitals		MoCA (out of 30)	ABC (%)	Mini-BESTest (out of 28)	TMT-B (sec)	9-HPT* (sec)	9-HPT** (sec)
				R HR (bpm)	R BP (mmHg)						
S01	F	24	R	49	102/59	30	93.4	28	58.2	16.9	20.6
S05	M	31	R	70	110/62	30	99.4	28	48.5	16.5	22
S07	M	24	R	77	126/76	27	95	27	53.4	22.6	18.5
S09	F	20	R	79	145/79	26	97.5	27	52.7	18.0	19.7

S10	F	24	R	86	104/73	30	94.4	28	56.2	17.6	18.0
S11	F	25	R	81	111/79	29	99.4	28	31.1	19.1	19.8
S12	F	23	R	62	115/70	25	91.9	28	70.6	24.1	23.5
S13	F	23	R	63	103/75	29	95.6	28	N/A	17.3	16.4
S16	F	24	R	61	113/64	29	98.1	28	49.9	18.9	19.7
Mean	N/A	24	R	68.6	114.3 / 70.8	28.3	96.1	27.8	52.6	19.0	19.8
St. Dev.	N/A	±3	R	±12.2	±13.66 / 7.48	±1.9	±2.7	±0.4	±1.1	±2.6	±2.1

Values presented are the mean and standard deviation. HI, Handedness Inventory; RHR, resting heart rate; ABC, Activities-Specific Balance Confidence Scale; Mini-BESTest, Mini Balance Evaluation Systems Test; MoCA, Montreal Cognitive Assessment; TMT – B, Trails Making Test – Part B; 9-HPT, 9-Hole Peg Test; N/A, not available; St. Dev., Standard Deviation. * Denotes dominant hand usage, **Denotes non-dominant hand usage.

Movement-based Priming & EEG Changes

Moderate intensity aerobic exercise resulted in a significant increase in high beta coherence between electrodes overlying IM1 and SMA ($t=3.08$, $p=0.018$). Change in IM1-SMA coherence were not driven by pre-post changes in high beta power in leads overlying IM1 ($p=0.91$) and SMA ($p=0.20$). Importantly, high beta IM1-SMA coherence did not differ between baseline and pre-priming EEG recordings ($p=0.83$) thus supporting stability in brain functional status prior to priming. Trends of decreased coherence between leads overlying IM1 and IPr ($p=0.10$) and between leads overlying IM1 and rM1 ($p=0.10$) were also observed. Aerobic-exercise priming did not elicit any changes in high beta power.

Cognitive-based Priming & EEG Changes

Cognitive-based priming did not elicit any changes in high beta coherence or power. Trends of decreased coherence between leads overlying rM1 and rPr ($p=0.08$) and increased coherence between leads overlying rM1 and rPMd ($p=0.08$) were observed. Attention status across participants remained stable across the priming bout as demonstrated by all participants correctly identifying the number of video clips of themselves walking on the treadmill.

Discussion

The purpose of this pilot study was to elucidate changes in neural function using EEG following two clinically feasible modes of priming. Our results suggest that a short bout of moderate

intensity aerobic exercise, not action observation, has the potential to increase coherence between cortical motor regions in the high beta frequency band, a range previously shown to be associated with motor function.^{34,35} Our findings underscore the notion that priming of the motor system subsequently modulates connectivity within a motor-specific neural network.

Several reasons may explain the observed increase in coherence between IM1 and SMA after aerobic exercise. The SMA is part of a motor-specific circuit involved in both upper and lower extremity movement.^{46,47} Work employing bilateral priming, a primarily upper extremity form of movement-based priming, demonstrates increased connectivity between M1 and SMA in adults as measured by non-invasive brain stimulation, i.e. transcranial magnetic stimulation.⁴⁷ Importantly, the SMA has been found to have a role in anticipatory postural adjustments important during step initiation of gait in healthy individuals.⁴⁶ Together, this evidence depicts the involvement of SMA in motor execution and control, and supports our finding of increased coherence between M1 and SMA.

Interestingly, we did not observe any other statistically significant changes in EEG power and coherence following aerobic priming. Other forms of movement-based priming have shown changes in cortical activity involving the primary motor cortex.^{5,48} It is important to note that the majority of movement-based priming involves the upper extremity. Hence, we surmise that the divergence between our findings and others may relate to different corticomotor drive between upper and lower extremity tasks.⁴⁹ For instance, in contrast to reaching, walking is a reciprocal activity and the discrepancy in corticomotor drive or neural substrate involvement between reciprocal and non-reciprocal activities is not fully understood at this time.⁴⁹ A recent study by Charalambous et al, did not observe changes in locomotor learning following aerobic priming in individuals post-stroke as measured by the adaptation rate to split belt treadmill changes.⁵⁰ Together, our findings and those of Charalambous demonstrate that the benefits of upper-extremity priming observed in other studies^{5,8} may not extrapolate to lower extremity priming.⁵⁰

This study also found no changes in EEG power and coherence following a brief bout of cognitive priming. There is conflicting evidence of neurophysiological change following cognitive priming in the literature. A study by Taub et al. found increased SMA activity, as measured using functional MRI and the blood oxygen level dependent (BOLD) signal, following motor imagery with action observation and motor imagery without the addition of action observation,

but not with action observation alone.⁵¹ Others that have examined action observation consistently found the SMA was part of the network of activation following action observation.⁵²⁻
⁵⁴ Our findings contrast this latter work.⁵²⁻⁵⁴ We surmise that methodological factors may contribute to these divergent findings. The possibility exists that priming may have modulated connectivity but not in the high beta frequency band. Findings by Kim et al. highlight the relevance of the alpha (8-13 Hz) frequency band.⁵⁵ Given the relatively brief duration of priming involved in our study, it is possible that multiple sessions of action observation priming are required to observe changes related to brain function. In a study by Kuk et al. that employed one minute of action observation priming over multiple sessions, investigators observed changes in cortical activation patterns related to the mirror neuron system beginning at the second session and improving with repeated exposure.¹³ Given the involvement of SMA in the planning of complex motor tasks,⁵⁶ including gait,⁴⁶ another important factor to consider is instructions (or lack thereof) provided to the subjects by the investigators prior to priming. Subjects were only instructed to watch the video of individuals walking while observing the number of times they saw themselves in the video. Without more specific instructions, it is unclear if the subjects were appropriately focused on the complexity of gait, possibly leading to variability in what the subjects chose to focus. Although our findings are in contrast to previous work regarding action observation and activity of the SMA, it is possible there are changes we did not observe due to methodological limitations described above.

This study contains several strengths including the examination of clinically feasible modes of priming involving the under-studied lower extremity along with the use of EEG to better understand changes in neural function following priming to complement previous work employing non-invasive brain stimulation. There are some additional limitations to address. As this was a pilot study, the sample size was small and homogenous, resulting in limited generalizability of the findings. Although we attempted to standardize the duration of priming between the two modes, aerobic priming required an average of an additional 3 minutes (178.83 seconds) of walking to ramp-up to their target HR. Another limitation requiring greater standardization between modes of priming. in the future is timing of the “immediately” post-priming EEG recording. It took about 2.5 minutes (153.13 seconds) longer to transition subjects from walking on the treadmill to the initiation of the EEG recording immediately post-intervention compared to the cognitive priming condition. This is especially important considering the “peak” of the effects of the priming intervention may vary depending on priming-mode and may not occur immediately after the intervention is implemented. For instance, Milani et al. found that

the peak impact for pharmacological priming to be between 12 to 16 minutes in healthy adults.²¹ Future studies should acquire a series of EEG recordings following the priming intervention to determine the optimal “window of time” when EEG coherence/power are most robust which may coincide with the administration of a subsequent motor task to elicit motor learning.

This work demonstrated that aerobic exercise increases brain connectivity in a motor relevant circuit in healthy adults. Heightened connectivity following aerobic priming may have important implications related to subsequent motor learning and, in a neurorehabilitation setting, motor re-learning. The next set of logical steps involve validating these findings in a larger independent sample and investigating aerobic exercise priming in both healthy aging adults and patient populations. Nevertheless, these results provide an exciting step toward understanding the neurological underpinnings of priming as they relate to the lower extremity.

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