

# A single bout of high-intensity aerobic exercise facilitates response to paired associative stimulation and promotes sequence-specific implicit motor learning

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<sup>2</sup>Department of Pediatrics, Faculty of Medicine, University of British Columbia, Vancouver, Canada; <sup>3</sup>Department of Medical Genetics, Faculty of Medicine, University of British Columbia, Vancouver, Canada; <sup>4</sup>Graduate Program in Neuroscience, Faculty of Medicine, University of British Columbia, Vancouver, Canada

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**Mang CS, Snow NJ, Campbell KL, Ross CJ, Boyd LA.** A single bout of high-intensity aerobic exercise facilitates response to paired associative stimulation and promotes sequence-specific implicit motor learning. *J Appl Physiol* 117: 1325–1336, 2014. First published September 25, 2014; doi:10.1152/jappphysiol.00498.2014.—The objectives of the present study were to evaluate the impact of a single bout of high-intensity aerobic exercise on 1) long-term potentiation (LTP)-like neuroplasticity via response to paired associative stimulation (PAS) and 2) the temporal and spatial components of sequence-specific implicit motor learning. Additionally, relationships between exercise-induced increases in systemic brain-derived neurotrophic factor (BDNF) and response to PAS and motor learning were evaluated. Sixteen young healthy participants completed six experimental sessions, including the following: 1) rest followed by PAS; 2) aerobic exercise followed by PAS; 3) rest followed by practice of a continuous tracking (CT) task and 4) a no-exercise 24-h retention test; and 5) aerobic exercise followed by CT task practice and 6) a no-exercise 24-h retention test. The CT task included an embedded repeated sequence allowing for evaluation of sequence-specific implicit learning. Slope of motor-evoked potential recruitment curves generated with transcranial magnetic stimulation showed larger increases when PAS was preceded by aerobic exercise (59.8% increase) compared with rest (14.2% increase,  $P = 0.02$ ). Time lag of CT task performance on the repeated sequence improved under the aerobic exercise condition from early (−100.8 ms) to late practice (−75.2 ms,  $P < 0.001$ ) and was maintained at retention (−79.2 ms,  $P = 0.004$ ) but did not change under the rest condition ( $P > 0.16$ ). Systemic BDNF increased on average by 3.4-fold following aerobic exercise ( $P = 0.003$ ), but the changes did not relate to neurophysiological or behavioral measures ( $P > 0.42$ ). These results indicate that a single bout of high-intensity aerobic exercise can prime LTP-like neuroplasticity and promote sequence-specific implicit motor learning.

neuroplasticity; aerobic exercise; motor learning; brain-derived neurotrophic factor

MULTIPLE STUDIES DEMONSTRATE that engaging in regular exercise has positive effects on cognitive function (11, 45). Complementary research indicates that engagement in a single bout of aerobic exercise can also positively impact cognitive function, with the most robust effects occurring on learning and memory processes (29, 45). For example, aerobic exercise performed immediately before task practice facilitated vocabulary learning in young healthy individuals (62) and enhanced image recall in healthy elderly individuals, as well as those with mild cognitive impairment (51). More recently, a high-intensity aerobic exercise bout performed immediately before or after

skilled motor practice increased long-term retention of the motor skill (24 h and 7 days after practice), suggesting that pairing aerobic exercise with motor practice has potential to facilitate motor learning (46). This finding has led to further speculation that pairing aerobic exercise with motor training may facilitate response to motor rehabilitation training after neurological injury (32, 45, 46). However, the mechanisms driving the effect of aerobic exercise on motor learning are not well understood. The present study was designed to investigate the “priming” effects of an acute bout of high-intensity aerobic exercise on neuroplasticity and implicit motor skill learning in young healthy individuals.

The immediate effects of aerobic exercise on memory may be driven in part by exercise-induced increases in neurochemicals, which facilitate long-term potentiation (LTP) (45, 53). Although ample work demonstrates systemic increases in catecholamines and neurotrophic growth factors immediately after aerobic exercise (6, 10, 62), limited work directly evaluates altered capacity for neuroplastic change evoked acutely by aerobic exercise. A continuous 0-burst stimulation (cTBS) protocol designed to suppress motor cortical excitability via long-term depression (LTD)-like mechanisms evoked a greater suppressive effect when preceded by a low-intensity bout of aerobic exercise, compared with a moderate-intensity bout or a period of rest (34). Recently, an acute bout of moderate-intensity aerobic exercise was found to facilitate response to paired associative stimulation (PAS) administered to increase motor cortical excitability via LTP-like mechanisms (53). Although the only study to demonstrate an effect of aerobic exercise on motor learning utilized a high-intensity exercise bout (46), the immediate effect of a high-intensity aerobic exercise bout on neuroplasticity has yet to be investigated. Importantly, aerobic exercise-induced alterations in neurochemicals, which can both up- and downregulate neuroplasticity, are dependent on exercise intensity (28, 34, 49, 62). Thus additional research is necessary to determine whether exercise-induced changes in LTP may underlie the effects of high-intensity aerobic exercise on motor learning.

Presently, only one study has evaluated the effect of acute aerobic exercise on motor learning (46). Motor learning is a complex process, involving multiple brain systems that support different aspects of skill acquisition (55). For example, motor learning can involve nonspecific improvements in motor control, as well as implicit (i.e., acquired without conscious awareness) sequence-specific improvements in performance (3, 35, 61). Additionally, motor performance can be decomposed into elements of temporal precision and spatial accuracy (3, 61). An improved understanding of which aspects of motor learning are

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acutely affected by aerobic exercise could provide insights into the brain regions primarily impacted by aerobic exercise, as well as whether aerobic exercise has different effects on the learning of different types of motor skills.

We hypothesized that an acute bout of high-intensity aerobic exercise would facilitate LTP-like neuroplasticity in a group of young healthy individuals. We used single-pulse transcranial magnetic stimulation (TMS) to test changes in corticospinal excitability evoked by a PAS paradigm designed to induce LTP-like effects (47, 56). PAS was preceded by either a period of rest or an acute bout of high-intensity aerobic exercise. Sequence-specific implicit motor learning was assessed in terms of temporal precision and spatial accuracy via practice of a joystick-based continuous tracking (CT) task that was preceded by either a period of rest or an acute bout of high-intensity aerobic exercise. As aerobic exercise triggers a cascade of neurobiological events that upregulate neurochemicals in multiple brain regions (12, 13), we hypothesized that an acute aerobic exercise bout before motor practice would facilitate both temporal and spatial implicit motor sequence learning, as reflected by improved performance from early practice to a 24-h retention test. Finally, we measured systemic levels of brain-derived neurotrophic factor (BDNF) immediately before and after aerobic exercise. BDNF is a neurotrophic growth factor that is involved in LTP and is susceptible to upregulation by aerobic exercise (1, 13, 28, 44). We hypothesized that aerobic exercise-induced increases in neuroplasticity and motor learning would be positively correlated with the upregulation of systemic BDNF following the aerobic exercise bout.

## METHODS

### Participants

Eight men and eight women between ages 19 and 33 (mean  $\pm$  SD;  $23.9 \pm 3.7$  yr) participated in this study. Participants had no known neurological disorders and were of adequate health to complete our exercise protocols. All participants gave written informed consent before testing. The Behavioural Research Ethics Board at the University of British Columbia approved all experimental procedures.

### Experimental Design

Each participant first completed a graded maximal exercise test. Every participant next completed six experimental sessions designed to assess the effects of a 20-min period of rest and a 20-min standardized bout of high-intensity cycling [aerobic exercise; 90% of maximal power output (PO) in watts] on both change in corticospinal excitability evoked by PAS and motor learning. The six experimental sessions included the following: 1) rest followed by PAS; 2) aerobic exercise followed by PAS; 3) rest followed by skilled motor practice using a joystick-based CT task and 4) a no-exercise 24-h retention test; and 5) aerobic exercise followed by CT task practice and 6) a no-exercise 24-h retention test. Capillary blood samples were collected via finger stick during the aerobic exercise sessions to determine blood lactate (BLa) response to the aerobic exercise bout, as well as serum levels of BDNF before and after the aerobic exercise bout. Session order was pseudo-randomized and performed at the same time of day ( $\pm 2$  h) for each participant to account for diurnal fluctuations in motor cortical excitability (58) and serum BDNF levels (5). On all testing days, participants were instructed to refrain from any exercise besides that involved in the experimental sessions. All sessions were separated by at least 48 h with two exceptions: retention tests were conducted  $24 \pm 2$  h following CT practice sessions, and there was a minimum washout period of 2 wk between CT practice under the

different experimental conditions (rest or aerobic exercise). The procedures are depicted in their experimental order in Fig. 1.

### Exercise Procedures

**Graded maximal exercise testing.** A maximal exercise test was conducted on a cycle ergometer (Ergoselect 200; Ergoline, Bitz, Germany), beginning with a workload (PO) of 100 W for men and 50 W for women, and was increased by 30-W increments every 2 min until exhaustion. Participants were instructed to maintain a pedaling cadence of 70–90 rotations per minute (rpm) and to remain seated throughout testing. During exercise testing, the following measurements were monitored: expired  $O_2$  and  $CO_2$  concentrations and air flow via a metabolic cart (TrueOne 2400; ParvoMedics, Sandy, UT), heart rate (HR) via a HR monitor (Polar Electro; Oy, Kempele, Finland), and Borg's 6–20 scale rating of perceived exertion (RPE) (2). Finger-stick BLa was determined immediately following the exercise test using an automated portable BLa analyzer and test strips (Lactate Pro; Arkray, Kyoto, Japan). Peak  $O_2$  consumption ( $\dot{V}O_{2peak}$ ) criteria included at least one of the following: a plateau in  $O_2$  uptake ( $\dot{V}O_2$ ) and HR with further increase in workload, a respiratory exchange ratio  $>1.1$ , a RPE  $>$ , BLa  $>10$  mmol/l, an inability to maintain a cadence of 70 rpm, and volitional exhaustion. Exercise testing results for each individual are presented in Table 1.

**Standardized acute aerobic exercise bout.** Maximal PO determined by the exercise test was used to inform prescription of a standardized acute aerobic exercise bout. The bout lasted 20 min and included a 5-min warmup at 50 W and self-selected cadence, followed by three 3-min sets of high-intensity cycling interspersed with 2 min of low-intensity cycling. The high-intensity intervals consisted of cycling at 90% of maximal PO from the final fully completed stage of the maximal exercise test, and the low-intensity intervals involved cycling at 50 W, always maintaining a cadence  $>70$  rpm. The aerobic exercise bout was based on previous work demonstrating systemic increases in neurochemicals with minimal long-term fatigue or dehydration (4, 62) and is similar to that previously employed by Roig et al. (46). Participants performed the aerobic exercise bout on two occasions: once immediately before PAS procedures and once immediately before CT practice.

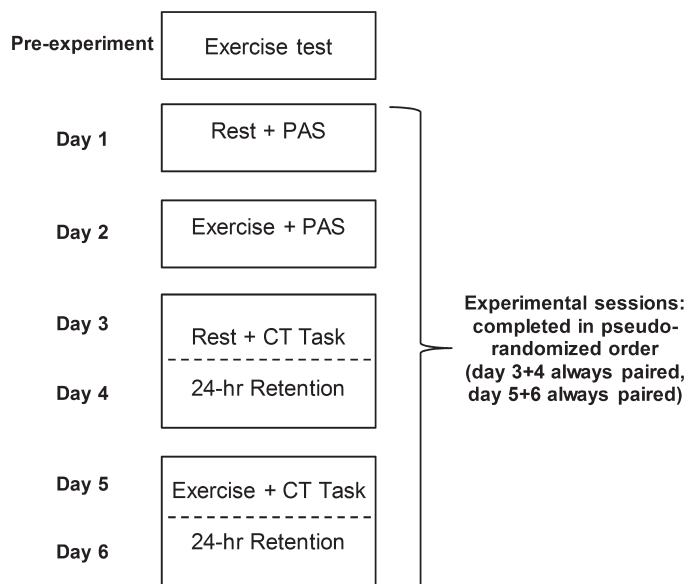


Fig. 1. Overview of experimental procedures. PAS, paired associative stimulation; CT, continuous tracking.

Table 1. Participant characteristics

Participant	Age	Sex	Dominant Hand	Exercise Test in Final Stage						Exercise Bout			
				$\dot{V}O_{2peak}$	PO	HR	RER	BLa	RPE	PO	HR	BLa	RPE
01	27	M	R	63.4	280	179	1.11	14.1	—	250	156	9.8	—
02	22	M	R	45.7	280	187	1.16	10.0	—	250	183	11.7	—
03	25	M	R	40.4	250	195	1.22	14.7	20	225	187	13.7	19
04	25	F	R	37.0	140	191	1.18	8.2	19	125	163	8.8	15
05	33	M	R	59.7	310	182	1.12	13.6	19	180	176	6.7	14.5
06	24	F	R	46.2	230	188	1.10	12.8	20	205	170	6.9	14
07	24	F	R	46.7	260	178	1.14	10.4	19	235	166	10.7	13
08	27	F	R	47.2	230	178	1.17	12.7	18	205	180	11.3	19
09	21	M	R	60.1	310	183	1.08	11.4	19	280	171	11.6	15
10	19	F	R	40.2	170	188	1.23	13.1	17	145	185	12.4	16.5
11	24	F	R	45.1	200	174	1.15	11.8	18	180	172	12.7	16.25
12	19	F	R	30.4	110	194	1.35	10.0	19	80	199	12.0	19.5
13	28	M	R	44.2	220	193	1.25	17.1	19	200	189	12.1	17.5
14	20	F	R	33.9	140	183	1.27	12.8	15	125	184	15.7	18
15	22	M	R	49.8	280	180	1.21	13.0	19	250	179	19.7	19
16	22	M	L	35.8	130	188	1.35	12.1	15	115	195	14.9	14

Power output (PO, in W) for the exercise bout was consistent across all 3 high-intensity intervals for each bout; the remaining values were collected at the end of the third (final) interval within an exercise bout. Heart rate (HR, in beats/min) and Borg's rating of perceived exertion (RPE) listed for the exercise bout are averages of the values collected on the 2 bouts (once for paired associative stimulation and once for the continuous tracking task). RPE was not collected during exercise for the first 2 participants.  $\dot{V}O_{2peak}$ , peak oxygen consumption (ml/kg per min); RER, respiratory exchange ratio; BLa, blood lactate (mmol/l).

### PAS Procedures

The following procedures were conducted with each participant under each experimental condition (rest and aerobic exercise).

**Electromyography.** Surface electromyography (EMG) was collected from 1 cm × 1 cm square surface recording electrodes (Coviden, Mansfield, MA) placed over the belly of the abductor pollicis brevis muscle (APB) of the nondominant hand. EMG signals were collected using LabChart software (LabChart 7.0; AD Instruments, Colorado Springs, CO) and were preamplified (1,000×) and band-pass filtered at 10–1,000 Hz with PowerLab amplification and EMG Systems (AD Instruments). Data for all evoked potentials were sampled at 2,000 Hz and recorded from 100 ms before to 400 ms after stimulus delivery.

**Median nerve stimulation.** Rectangular pulses of 0.2-ms duration were delivered over the median nerve at the wrist of the nondominant hand using a constant current stimulator (DS7A; Digitimer, Hertfordshire, UK). Immediately before motor-evoked potential (MEP) recruitment curve collection (see below), electrical stimulation intensity was increased over 5–10 stimuli from below motor threshold to 1.5 times the minimum current to evoke the maximal motor wave ( $M_{max}$ ) in APB.  $M_{max}$  was determined as the largest peak-to-peak amplitude M-wave evoked in APB in these stimuli.  $M_{max}$  is a stable measure of muscle activity during maximal muscle fiber recruitment (7) and was used as a reference from which to normalize MEPs evoked by TMS (34).

**TMS.** TMS was delivered using a figure-of-eight coil (Magstim 70 mm P/N 9790; Magstim, Carmarthenshire, UK) and Magstim 200<sup>2</sup> stimulator (Magstim) over the nondominant APB motor cortical representation. Before the rest period or aerobic exercise bout, the coil was moved over the motor cortex to find the site that elicited the largest amplitude MEP at the lowest stimulation intensity for APB. With the use ofBrainsight image-guided neuronavigation software (Rogue Resolutions, Montréal, Quebec, Canada), this stimulation site was recorded and used to maintain orientation for all TMS delivery. All MEPs were evoked at rest. Resting motor threshold (RMT) was determined by finding the lowest stimulation intensity that evoked MEPs of at least 50  $\mu$ V in 5 out of 10 consecutive trials (48). An MEP recruitment curve (baseline) was then conducted to determine corticospinal excitability via measurement of the amplitude of MEPs elicited at varying TMS intensities. Ten stimuli were delivered at 0.25 Hz in a random order at intensities ranging from 90–150% of RMT,

in 10% increments for a total of 70 stimuli collected over ~5 min. Recruitment curves were collected using the same stimulation site and intensities immediately pre-PAS (beginning within 5 min after rest/exercise) and post-PAS (beginning within 2 min after PAS). Including the delivery of PAS, all assessments were completed within ~45 min following the rest period or exercise bout.

MEP recruitment curve data were processed using a custom MATLAB script (Mathworks, Natick, MA). To ensure all MEPs were obtained at rest, MEPs were inspected post hoc and discarded if EMG activity during the 100 ms before the TMS pulse exceeded two SD of the average prestimulus signal. Less than 0.4% of all responses were removed from further analyses based on this criterion. Plots of stimulation intensity (%RMT) by MEP amplitude (peak-to-peak amplitude expressed as % $M_{max}$ ) were then constructed for each individual at each time point and under each condition. Previous studies have fit MEP recruitment curve data with both linear (41, 47) and sigmoidal (15, 33) functions. The range of stimulation intensities (90–150% RMT) was chosen to capture the ascending portion of the MEP recruitment curve and, upon visual inspection, appeared to be best suited to a linear fit. This was verified by conducting leave-one-out cross-validation procedures on all recruitment curves, which yielded, on average, a lower mean squared error for the linear ( $8.16 \pm 10.31$ ) vs. sigmoidal ( $11.48 \pm 14.28$ ) functions. The linear function fit the data with an average  $R^2$  of  $0.71 \pm 0.21$ . A larger recruitment curve slope value following PAS indicated an increase in corticospinal excitability.

**PAS.** Electrical stimulation was delivered over the median nerve of the nondominant limb with 0.2-ms duration pulses at 300% perceptual threshold (PT) 25 ms before the delivery of TMS. TMS was applied over the APB motor cortical representation for the nondominant limb at an intensity that evoked a MEP of ~1 mV ( $SI_{1mV}$ ). In total, 450 paired stimuli were delivered at 0.25 Hz (30 min of stimulation). Similar PAS protocols have previously been shown to enhance corticospinal excitability at rest (47, 56).

### CT Task Procedures

CT task practice took place following both the rest and aerobic exercise conditions for each participant, with at least 2 wk between conditions. CT task practice involved manipulation of a finger joystick (Fig. 2; Current Designs, Philadelphia, PA) with the thumb of the nondominant hand. The joystick was used to move a cursor up and



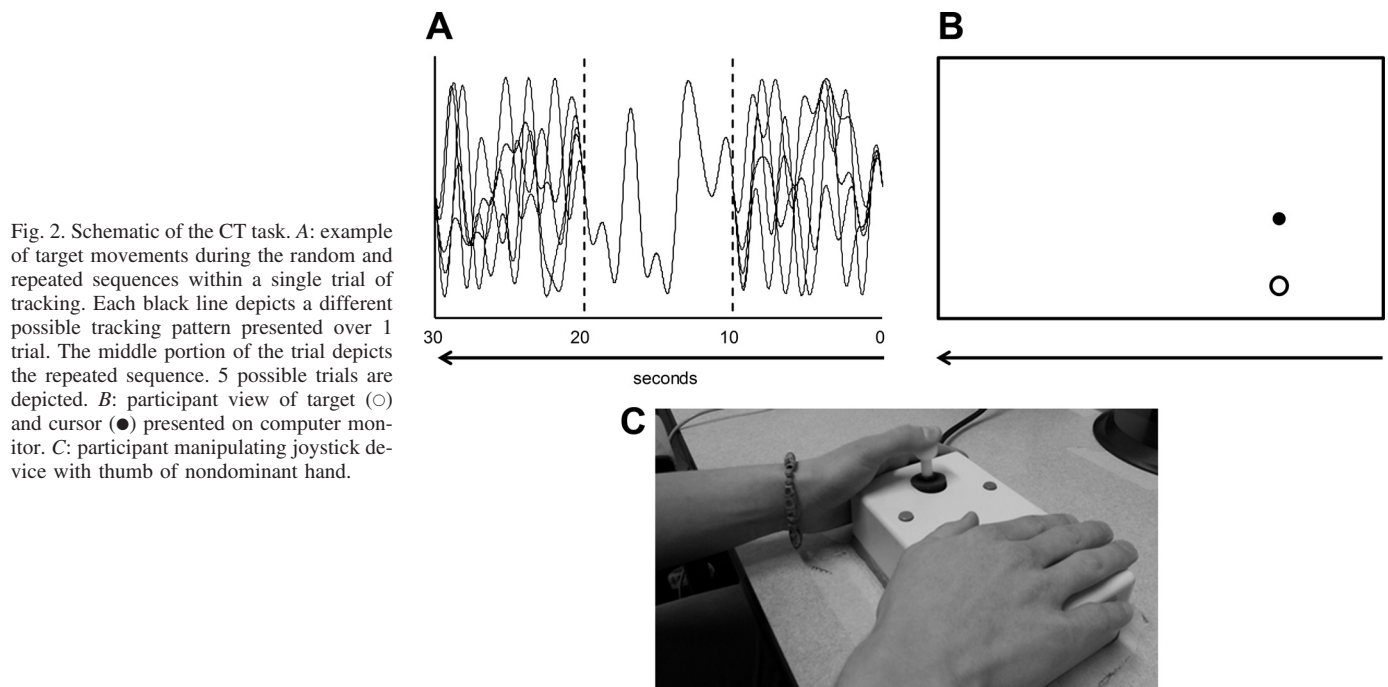


Fig. 2. Schematic of the CT task. *A*: example of target movements during the random and repeated sequences within a single trial of tracking. Each black line depicts a different possible tracking pattern presented over 1 trial. The middle portion of the trial depicts the repeated sequence. 5 possible trials are depicted. *B*: participant view of target (○) and cursor (●) presented on computer monitor. *C*: participant manipulating joystick device with thumb of nondominant hand.

down to track the vertical path of a target moving at a constant horizontal velocity from the right to the left of a computer screen. Joystick position sampling and all stimuli were presented at 50 Hz using custom software developed on LabView (v. 9.0; National Instruments, Austin, TX). The CT task was presented in 30-s trials, preceded by a 2-s normalization period, where the cursor became zeroed to the target. For every 30-s trial, the first and last 10 s contained a random sequence, while the middle 10 s contained a repeated sequence that was identical across practice and retention blocks. Random and repeated sequences were controlled for difficulty level in terms of range of motion and velocity of the target movements (61). Participants were not informed of the existence of a repeated sequence but instructed to track the target with the cursor as accurately as possible on each occasion. The inclusion of repeated and random sequences allows separation between improvements in motor control (random sequences) and those associated with sequence-specific implicit learning (repeated sequences) (3, 35, 61). In the experimental sessions involving CT task practice, participants completed one trial of the CT task (30 s of movement) before the rest period or the aerobic exercise bout for task familiarization. For CT practice following rest or the aerobic exercise bout, participants completed two blocks of 10 trials, for a total of 10 min of CT practice. The following day ( $24 \pm 2$  h after motor practice), participants completed another single block of CT trials (delayed-retention test).

For each participant, the control of the joystick was reversed between rest and aerobic exercise conditions, such that left and right joystick movements resulted in up and down cursor movements for one condition and down and up cursor movements for the other condition. Participants were informed of the direction of joystick control at the beginning of each CT practice and retention session. Additionally, repeated sequences presented for each condition were reversed, such that the sequences differed but shared equivalent difficulty. The order of presentation of conditions (rest and aerobic exercise), joystick control (left-up, right-down vs. left-down, right-up) and sequences (regular or reversed) were balanced across the sample.

Following the final retention test, participants were tested for explicit recognition of the repeated sequences within the CT task from both conditions (rest and aerobic exercise). For the recognition testing, participants viewed a series of 13 CT trials, seven of which

included only random sequences and six of which included repeated sequences from the rest and aerobic exercise sessions. A group average of eight or more correctly identified sequences (4 of the 7 random sequences and 4 of the 6 repeated sequences) indicates that explicit knowledge of the repeated sequence was acquired (3, 35, 61).

CT task data were processed using a custom MATLAB script (Mathworks). Root mean squared error (RMSE) was calculated for each sequence. RMSE was separated into temporal and spatial error components using a cross-correlation analysis (3). Time lag of tracking represents the temporal distance from the target in milliseconds, with more negative numbers indicating that the cursor lags further behind the target. Removal of the calculated lag from the tracking signal before calculating the tracking error allowed for determination of spatial tracking error or shifted RMSE (3, 61). The time lag and shifted RMSE were then considered separately for the first and second random sequences combined (i.e., first and last 10 s of a trial) and the repeated sequence.

#### Serum BDNF

In the experimental session involving aerobic exercise followed by CT task practice, a 100- $\mu$ l capillary blood sample was drawn by finger stick and collected using a microvette capillary blood collection tube (Sarstedt, Numbrecht, Germany) immediately before and after the aerobic exercise bout. Participants were instructed not to eat within 30 min, exercise or drink coffee within 24 h, or drink alcohol or smoke within 48 h of this session (5). These samples were placed on wet ice immediately following collection and allowed 30 min to clot. The samples were then centrifuged at 1,000  $g$  for 15 min, and serum was aliquoted into 0.6-ml aliquots and stored at  $-80^{\circ}\text{C}$ . Serum BDNF concentrations were measured in duplicate by technicians blinded to sample time points using a Quantikine (R&D Systems, Minneapolis, MN) sandwich ELISA kit according to the manufacturer's instructions. All samples were assayed at the same time in a single, batched analysis.

#### Statistical Analyses

*PAS.* To determine whether  $M_{\text{max}}$  amplitude changed across time in each experimental session, a one-way repeated-measures ANOVA

was conducted for each condition with the factor time (baseline, pre-PAS, and post-PAS). PAS parameters were also tested for any potential differences between conditions (rest and aerobic exercise). Separate paired *t*-tests were performed to compare the 300% PT stimulation intensity (mA), RMT (% mean TMS output), and SI<sub>1mV</sub> intensity (% mean TMS output) between the rest and aerobic exercise conditions. An additional paired *t*-test was conducted to determine whether MEP recruitment curve slope was well matched between the rest and aerobic exercise conditions at the pre-PAS time point.

The percent change in linear slope of the recruitment curves from the baseline to pre-PAS measurements and the pre-PAS to post-PAS measurements was calculated and used as the dependent variable for analysis of the effects of PAS. A two-way repeated-measures ANOVA with the factors condition (rest, aerobic exercise) and time (baseline to pre-PAS, pre-PAS to post-PAS) was then conducted.

**CT task.** For each trial, the lag and shifted RMSE were determined separately for the random sequences and the repeated sequence. For the first random sequence (i.e., first 10 s of a trial), the first trial of the CT blocks was excluded from the analyses, as it included the first movement of a block and, as such, commonly showed higher error relative to the rest of the block. As such, the second trial was considered the first trial of a practice block when determining error for the first random sequence (i.e., first 10 s of a trial). Next, the first three trials of the first practice block (early practice), the last three trials of the second practice block (late practice), and the first three trials of the retention block (retention) were averaged for the two random sequences together and the repeated sequence separately. Two separate three-way repeated-measures ANOVAs with dependent variables lag and shifted RMSE were then conducted with factors condition (rest, aerobic exercise), sequence (random, repeated), and time (early practice, late practice, retention).

**Serum BDNF and correlation analyses.** A paired *t*-test was conducted to determine whether there was a change in serum BDNF concentration from pre- to post-aerobic exercise. Simple bivariate correlation analyses (Pearson's *r* or Spearman's *r<sub>s</sub>*) between the following variables were conducted: percent change in serum BDNF concentration from before to after aerobic exercise, percent change in linear recruitment curve slope from pre- to post-PAS for the aerobic exercise condition and, based on the results of the CT task analysis, percent change in lag on the repeated sequence from practice blocks to retention for the aerobic exercise condition. Bivariate correlation analyses were also conducted between the difference in percent change in linear recruitment curve slope between rest and exercise conditions and the difference in percent change in lag on the repeated sequence from practice blocks to retention between the rest and exercise conditions. These analyses were conducted to determine whether those individuals with greater facilitation of PAS effects following exercise were the same as those that showed greater facilitation of sequence-specific motor learning following exercise.

Following visual inspection of the data and objective testing using the Shapiro-Wilk test, all data were found to be normally distributed ( $W \geq 0.894$ ,  $P \geq 0.06$ ) except the percent change in serum BDNF ( $W = 0.793$ ,  $P < 0.01$ ). For all statistical tests, significance level was  $P < 0.05$ . For all ANOVAs, post hoc analyses (Fisher's least-significant-difference tests) were conducted where appropriate. All descriptive statistics are reported as means  $\pm$  SD. All statistical analyses were conducted using SPSS software (SPSS 21.0; IBM, Armonk, NY).

## RESULTS

### PAS

$M_{\max}$  did not change across time (baseline, pre-PAS, and post-PAS) in either the rest [ $f_{(2, 28)} = 1.45$ ,  $P = 0.25$ ] or aerobic exercise [ $f_{(2, 28)} = 0.25$ ,  $P = 0.78$ ] conditions. Additionally, 300% PT [ $t_{(15)} = -0.28$ ,  $P = 0.78$ ], RMT [ $t_{(15)} =$

$-1.57$ ,  $P = 0.14$ ], SI<sub>1mV</sub> intensities [ $t_{(15)} = -0.09$ ,  $P = 0.93$ ], and pre-PAS MEP recruitment curve slope [ $t_{(15)} = -0.11$ ,  $P = 0.91$ ] were not different between the rest and aerobic exercise conditions. These analyses indicate that, when considering the entire study sample, there were no differences in PAS procedures or pre-PAS recruitment curve slope across conditions (rest and aerobic exercise).

Figure 3 shows MEP recruitment curve plots and mean MEP waveforms collected at all intensities of the recruitment curves pre- and post-PAS for each condition for a representative participant. Figure 4 depicts changes in MEP recruitment curve slope evoked by PAS across the group for both rest and aerobic exercise conditions. The two-way repeated-measures ANOVA detected a significant main effect of time [ $f_{(1, 15)} = 6.86$ ,  $P = 0.02$ ] and a significant condition by time interaction [ $f_{(1, 15)} = 7.86$ ,  $P = 0.01$ ]. There was no main effect of condition [ $f_{(1, 15)} = 1.18$ ,  $P = 0.30$ ]. To determine whether increases in recruitment curve slope following PAS were statistically significant under each condition, post hoc comparisons utilized the baseline to pre-PAS change in recruitment curve slope under the rest condition as a control assessment (i.e., change in recruitment curve slope when no intervention is administered). The results demonstrate that, under the rest condition, the change in slope from pre- to post-PAS ( $14.18 \pm 32.70\%$ ) was not different from the change in slope from baseline to pre-PAS under the rest condition ( $7.59 \pm 34.11\%$ ,  $P = 0.69$ ), suggesting that PAS preceded by rest did not have a significant effect on recruitment curve slope. In contrast, under the exercise condition, the change in slope from pre- to post-PAS ( $59.81 \pm 73.49\%$ ) was significantly greater than the change from baseline to pre-PAS under the rest condition ( $7.59 \pm 34.11\%$ ,  $P = 0.001$ ), suggesting that PAS preceded by exercise significantly increased recruitment curve slope. Moreover, the change in recruitment curve slope from pre- to post-PAS was significantly greater when PAS was preceded by exercise than by rest ( $P = 0.02$ ). Finally, the change in recruitment curve slope from the baseline to pre-PAS time points was not significantly different between the rest and aerobic exercise conditions ( $P = 0.38$ ), indicating that aerobic exercise itself did not have a significantly different effect on MEP recruitment curve slope than the period of seated rest.

### CT Task

Figure 5, A and B, shows trial-by-trial time lag of tracking for repeated and random sequences under both the rest and aerobic exercise conditions for a single subject. Figure 6A shows the group averages for time lag of tracking from early practice, late practice, and retention for the rest and aerobic exercise conditions.

With time lag as the dependent variable, a three-way repeated-measures ANOVA revealed a significant main effect of sequence [ $f_{(1, 15)} = 16.27$ ,  $P = 0.001$ ], a significant main effect of time [ $f_{(2, 30)} = 5.70$ ,  $P = 0.01$ ], and a significant three-way condition by sequence by time interaction [ $f_{(2, 30)} = 3.39$ ,  $P = 0.04$ ]. The main effect of condition was not significant [ $f_{(1, 15)} = 2.04$ ,  $P = 0.17$ ]. Post hoc analyses indicated that, under the rest condition, participants' time lag of tracking did not significantly improve from early to late practice or early practice to retention for either the random ( $P > 0.05$ ) or repeated sequences ( $P > 0.16$ ). In contrast, CT time lag performance after

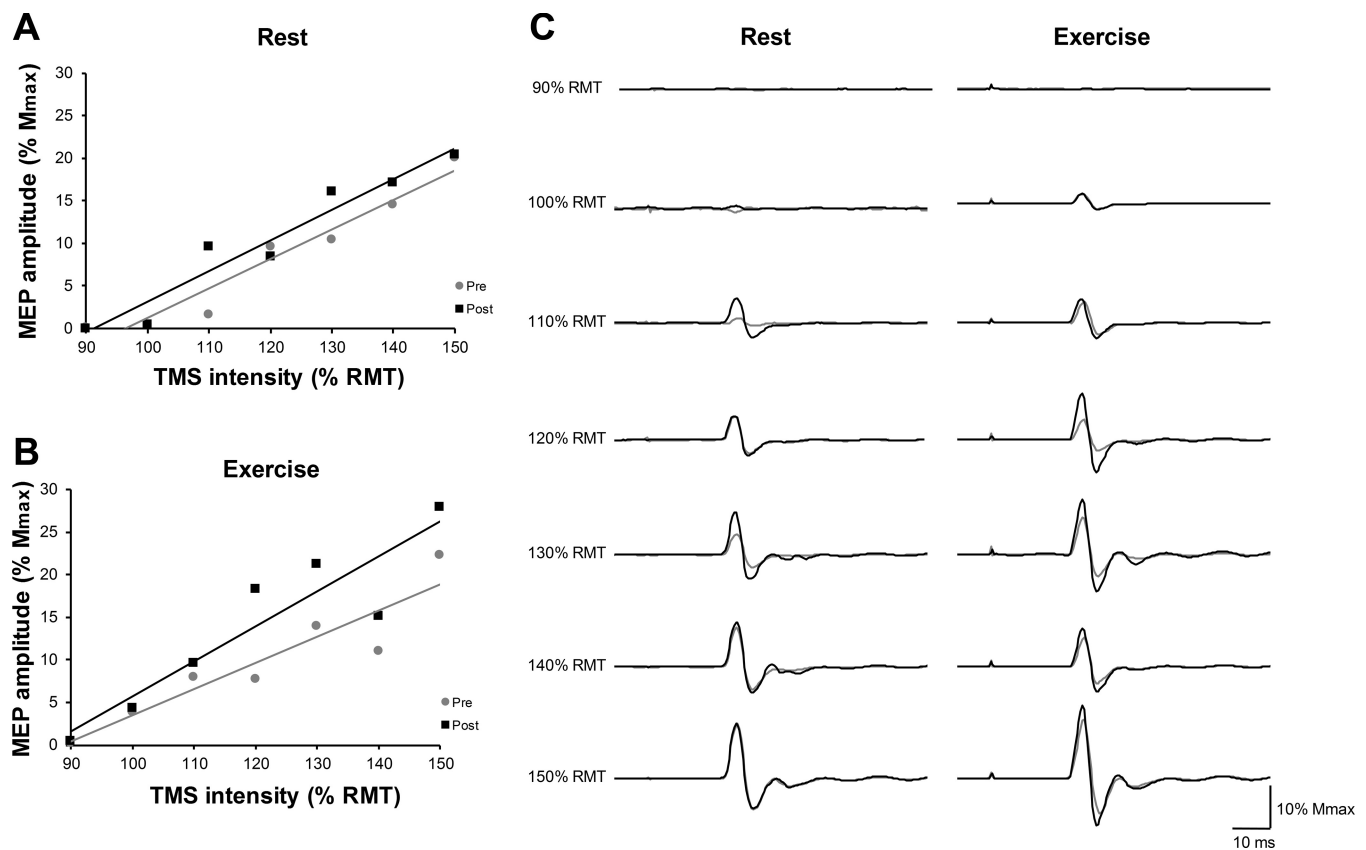


Fig. 3. Changes in corticospinal excitability evoked by PAS preceded by rest and exercise in a single subject. *A* and *B*: motor-evoked potential (MEP) recruitment curves collected pre-PAS (gray) and post-PAS (black) for each condition (rest and exercise). *C*: average raw MEP waveforms ( $n = 10$  MEPs) elicited pre-PAS (gray) and post-PAS (black) for each condition (rest and exercise) at each transcranial magnetic stimulation (TMS) intensity. RMT, Resting motor threshold.

the aerobic exercise bout did not change for random sequences ( $P > 0.22$ ) but improved significantly for the repeated sequence from early ( $-100.83 \pm 52.10$ ) to late practice ( $-75.21 \pm 45.57$ ;  $P < 0.001$ ), and this improvement was maintained at retention ( $-79.17 \pm 42.28$ ;  $P = 0.004$ ). Furthermore, time lag was significantly faster for repeated compared with random sequences at both late practice ( $P = 0.001$ ) and retention ( $P = 0.001$ ) for the exercise condition. Moreover, time lag performance of the repeated sequences was not different between conditions during early practice ( $P = 0.95$ ) but significantly faster under the aerobic exercise condition at late practice ( $P = 0.03$ ) and retention ( $P = 0.02$ ). These results demonstrate that sequence-specific learning of the temporal aspect of the CT task occurred when practice was preceded by aerobic exercise but not rest.

Figure 5, *C* and *D*, shows trial-by-trial spatial error via shifted RMSE for the repeated and random sequences under both rest and aerobic exercise conditions for a single subject. Figure 6*B* shows the group averages for shifted RMSE across practice and retention under the rest and aerobic exercise conditions. The inlaid plot shows the effects of time and sequence when collapsed across both conditions (rest and aerobic exercise).

The three-way repeated-measures ANOVA with shifted RMSE as the dependent measure yielded a significant main effect of sequence [ $f_{(1, 15)} = 6.01$ ,  $P = 0.003$ ] and a significant main effect of time [ $f_{(1, 15)} = 14.31$ ,  $P = 0.001$ ]. There were no main effects of condition [ $f_{(1, 15)} = 0.21$ ,  $P = 0.66$ ] or

interactions (all  $P > 0.05$ ). Post hoc analyses of the sequence effect (collapsed across conditions and time) showed that shifted RMSE of tracking on the random sequence was on average worse than performance on the repeated sequence ( $P = 0.003$ ). Post hoc analyses of the effect of time (collapsed across conditions) demonstrated that performance improved on average from early to late practice ( $P = 0.01$ ) and from both early and late practice to retention ( $P = 0.001$  and  $P = 0.002$ , respectively). Further analyses indicated that random and repeated-sequence spatial error was not significantly different during early ( $P = 0.61$ ) or late practice ( $P = 0.07$ ) but that performance on repeated sequences was significantly better than on random sequences at retention ( $P = 0.04$ ). These results indicate that implicit sequence-specific learning of the spatial aspect of the CT task occurred with practice but was not affected by condition (rest or aerobic exercise).

Across the group, participants did not demonstrate explicit knowledge of a repeated sequence during the recognition testing. The sequences were correctly identified at a level consistent with chance ( $7.2 \pm 2.1/13$  or  $55.4 \pm 16.5\%$  of the sequences).

#### Serum BDNF and Correlations

In a paired *t*-test analysis comparing pre- and postexercise blood samples, individual serum BDNF concentrations were increased on average by 3.4-fold following the aerobic exercise bout [ $5,258 \pm 3,258$  pg/ml to  $11,918 \pm 6,404$  pg/ml;  $t_{(14)} =$

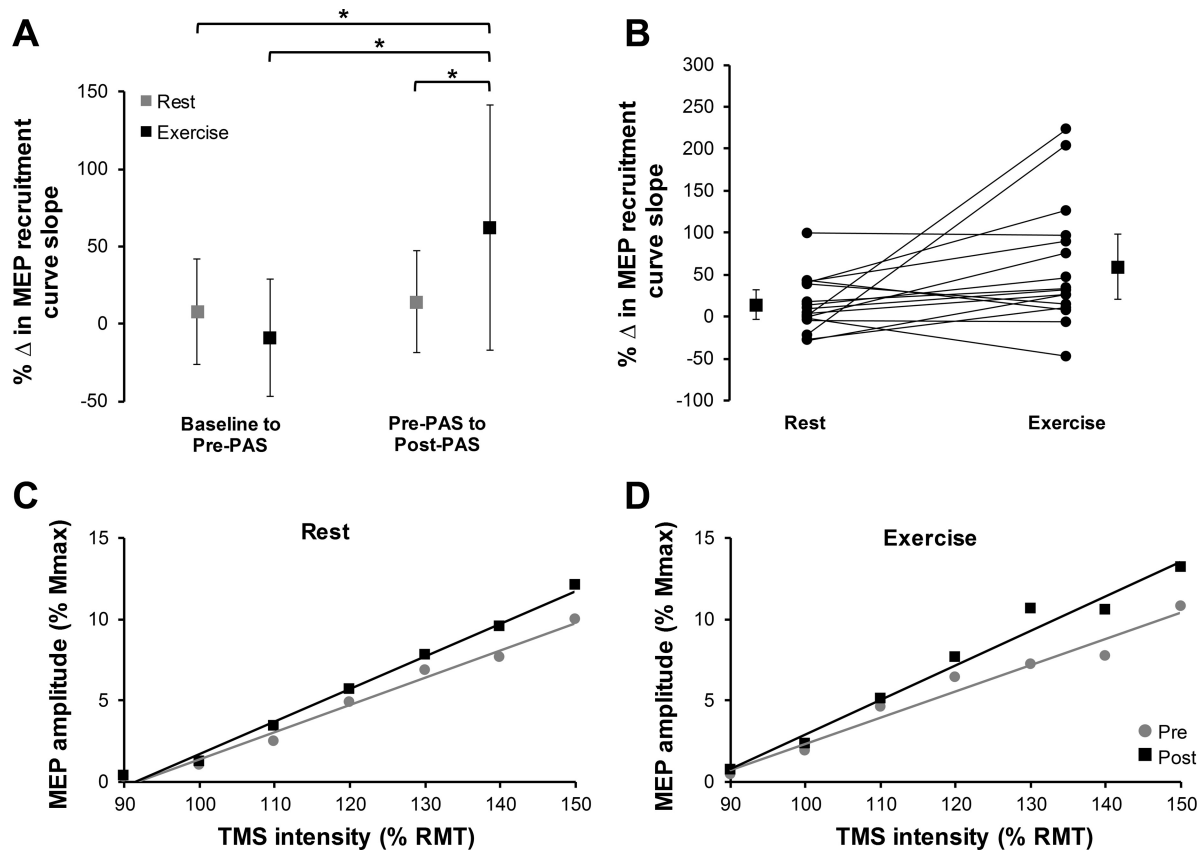


Fig. 4. Changes in corticospinal excitability evoked by PAS preceded by rest and exercise across the group. **A**: percent change in linear slope of MEP recruitment curves from baseline to pre-PAS and pre-PAS to post-PAS for the rest and exercise conditions when averaged across the group. Error bars represent 1 standard deviation. Horizontal bars and asterisks indicate statistically significant differences ( $P < 0.05$ ). **B**: percent change in MEP recruitment curve slope from pre-PAS to post-PAS under the rest and exercise conditions for each participant. Unlinked data points represent the mean percent change across the group under each condition (as shown also by bar graph in **A**). Error bars around the unlinked data points demonstrate the 95% confidence interval for percent change in recruitment curve slope. **C** and **D**: MEP recruitment curves with MEP amplitudes averaged across the group for all TMS intensities pre-PAS and post-PAS for the rest and exercise conditions, respectively.

$-3.61$ ,  $P = 0.003$ ]. However, there were no significant correlations between the change in serum BDNF concentration with change in linear recruitment curve slope for the aerobic exercise condition ( $r_s = -0.17$ ,  $P = 0.54$ ) or with change in lag on the repeated sequence from practice blocks to retention for the aerobic exercise condition ( $r_s = -0.15$ ,  $P = 0.59$ ). The change in recruitment curve slope and lag on the repeated sequences under the aerobic exercise condition were not correlated ( $r = -0.20$ ,  $P = 0.48$ ). Finally, the difference in percent change in linear recruitment curve slope between rest and exercise conditions and the difference in percent change in lag on the repeated sequence from practice blocks to retention between the rest and exercise conditions were not correlated ( $r = 0.42$ ,  $P = 0.11$ ).

## DISCUSSION

Our findings support the hypothesis that an acute bout of high-intensity aerobic exercise facilitates LTP-like neuroplasticity in the human motor system. In the same individuals, aerobic exercise before motor practice promoted sequence-specific implicit motor learning associated with improvements in temporal precision of continuous tracking. The aerobic exercise bout also increased systemic levels of BDNF, but these increases did not relate to the neurophysiological or

behavioral data. Overall, these findings imply that modulation of LTP-like neuroplasticity may underpin high-intensity aerobic exercise-induced improvements in implicit motor learning.

### A Single Bout of Aerobic Exercise Facilitates Response to PAS

Recent studies demonstrate that aerobic exercise can modulate neuroplasticity in the motor system (34, 53). For example, a moderate-intensity bout of cycling enhanced the LTP-like effects of a PAS protocol on corticospinal excitability for a muscle in the hand (53), and a low-intensity bout of cycling enhanced the LTD-like effects of a cTBS protocol on corticospinal excitability for a muscle of the hand (34). Both LTP and LTD are key neural processes involved in learning and memory, which respectively drive the strengthening of neural pathways as a memory is initially formed and then the focusing or pruning of neural pathways as preferential pathways develop (63). The rapid effects of PAS and cTBS suggest that these protocols trigger the early stages of such neuroplasticity that are dependent on chemical, rather than structural, changes at the synapse. Likewise, the systemic levels of a number of neurochemicals, such as dopamine, norepinephrine, and BDNF, which are known to influence motor cortical plasticity (26, 36, 43), are also upregulated with acute aerobic exercise (6, 10, 62). Sys-



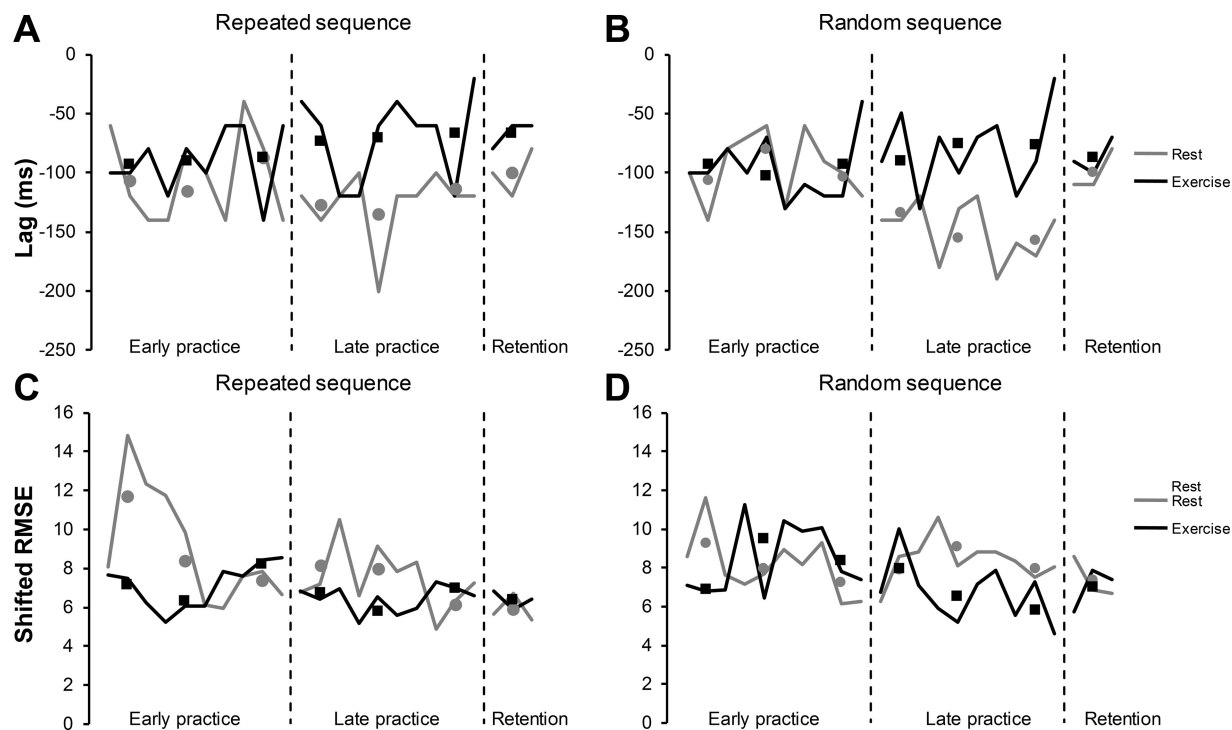


Fig. 5. CT task data collected from a single subject when practice was preceded by rest (gray) and exercise (black). CT performance in terms of temporal error (lag behind the target) (*A* and *B*) and in terms of spatial error corrected for the contribution of time lag (shifted root mean squared error, RMSE) (*C* and *D*). For *A* and *B*, more negative lag values reflect greater temporal error. *A* and *C* demonstrate repeated sequence performance, whereas *B* and *D* show the random sequence performance. Solid lines demonstrate performance on each trial, and data points represent performance averaged over 3–4 trials. Vertical dashed lines indicate changes in the CT block (early practice, late practice, and 24-h retention block).

temic increases in dopamine were observed both immediately and 30 min following exercise (62). Similarly, reports of systemic increases in BDNF occur as late as 60 min after exercise (28). Although increases in such neurochemicals are greater with higher-intensity exercise (28, 62), increasing intensities of exercise also induce higher levels of cortisol, a steroid hormone that has negative effects on plasticity in motor cortex (49). This finding has led to a focus in the recent literature on the effects of moderate- or low-intensity exercise on neuroplasticity (34, 53); however, previous work demonstrated that higher-intensity aerobic exercise facilitated vocabulary learning to a greater extent than moderate-intensity exercise (62). Likewise, the only study to demonstrate acute exercise effects on motor learning utilized a high-intensity exercise bout (46). The present study adds to the literature by showing that a single bout of high-intensity cycling can also facilitate LTP-like neuroplasticity evoked by PAS for a muscle of the hand. The time frame for the delivery of the PAS protocol (30-min duration, commenced within 5 min after exercise) and the intensity of the exercise align with a neurochemical mechanism for the exercise effect. As cortisol was not measured, we cannot speculate on how it was affected by exercise or whether it may have modulated our effects.

Additional research has investigated how an acute bout of aerobic exercise impacts the activity of intracortical circuits in motor cortical representations of nonexercised upper limb muscles. Smith and colleagues (54) reported a reduction in short-interval intracortical inhibition (SICI) in a small hand muscle immediately and 15 min after low-moderate- and moderate-high-intensity cycling. Other work demonstrated a reduc-

tion in SICI and an increase in intracortical facilitation (ICF) in a nonexercised upper limb muscle immediately and 30 min following a bout of moderate-intensity exercise (52). The extent of SICI is thought to reflect  $\gamma$ -aminobutyric acid activity (9), for which reduced activity is strongly implicated in the induction of LTP (21) and motor cortical plasticity (64). Similarly, ICF is thought to depend on activity of glutamatergic interneurons and *N*-methyl *D*-aspartate receptors (30), which are also key players in LTP-like plasticity. Given the modulation of these intracortical networks by exercise, and their involvement in LTP-like mechanisms, it is likely that such changes contribute to the observed effect of high-intensity exercise on responsiveness to PAS. Moreover, modulation of intracortical networks has been shown to persist for at least 30 min after exercise (52), which indicates that such changes would have been sustained during the administration of the PAS protocol in the present experiments.

The lack of change in MEP recruitment curve slope immediately following PAS under the rest condition in the present experiments was not expected but is consistent with recent work by Singh et al. (53), in which PAS preceded by rest facilitated MEP recruitment curves 30 min after but not immediately following the delivery of the PAS. Other studies have also shown a greater effect of PAS 30 min following the stimulation compared with immediately after (8, 14, 42). Thus, by only collecting MEP recruitment curves immediately following PAS, we may have missed the effect of PAS under the rest condition. Regardless, our findings demonstrate that a bout of high-intensity aerobic exercise potentiated the immediate response to PAS compared with a period of rest and are



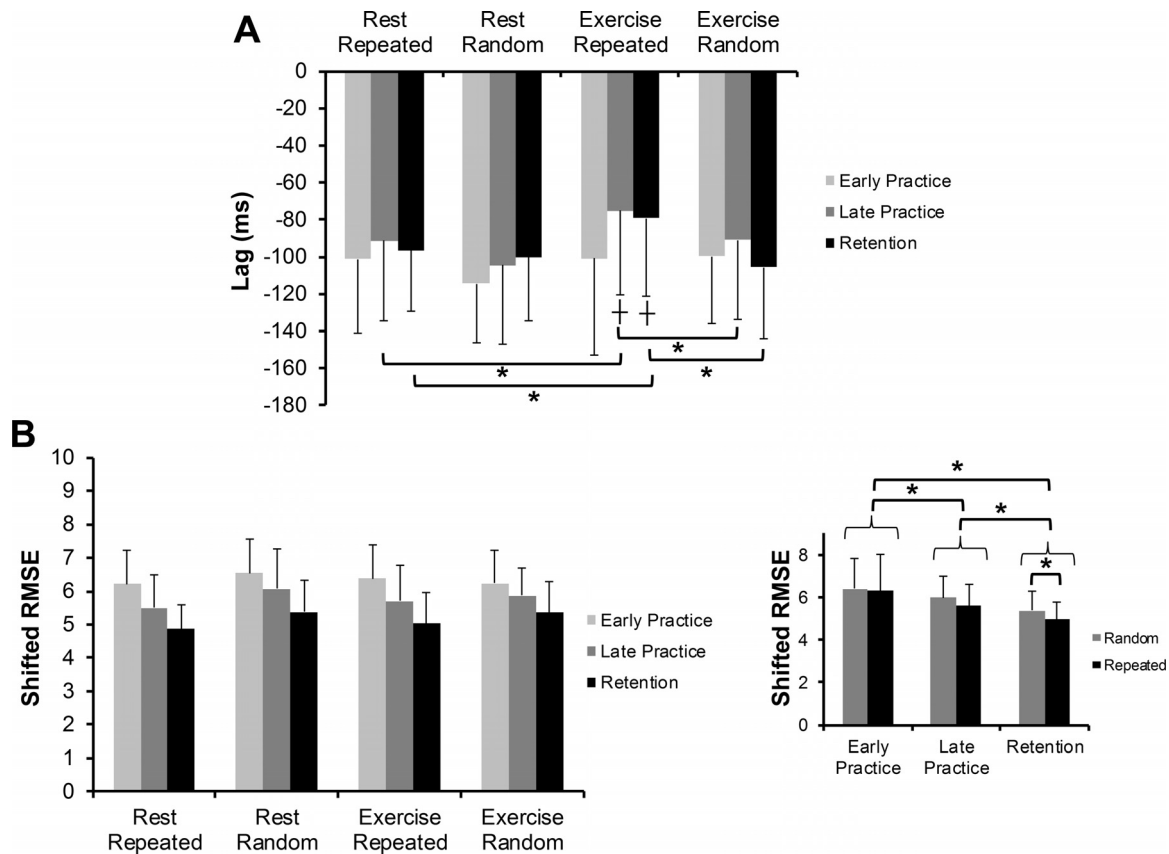


Fig. 6. CT task performance in terms of temporal error (lag, *A*) and spatial error corrected for time lag (shifted RMSE, *B*) when averaged across the group. In *A*, more negative lag values reflect greater temporal error. *B*, right: effects of time and sequence on shifted RMSE detected by the statistical analyses. Early practice refers to the beginning of practice block 1, late practice to the end of practice block 2, and retention to the beginning of the 24-h retention block. Error bars represent 1 standard deviation. †Statistically significant difference from early practice ( $P < 0.05$ ). Horizontal bars and asterisks indicate statistically significant differences between values ( $P < 0.05$ ).

consistent with work investigating the effects of moderate-intensity exercise (53). An additional factor that may have impacted the present results relates to exercise-induced arousal and attention. The magnitude of the effect of PAS on corticospinal excitability has previously been shown to be highly dependent on attention to the stimuli (57). Presently, participants were not provided with any explicit instructions regarding attention to the stimuli in either condition. Although participants did not report any differences in their level of attention between sessions, it is plausible that an increase in arousal after exercise (29) enhanced participants' attentiveness to the stimuli and that this increase in attention contributed to the modulation of the response to PAS. However, Singh et al. (53) recently demonstrated a similar effect of moderate-intensity exercise on response to PAS when attention was monitored by instructing participants to count the stimuli under both rest and exercise conditions. Finally, although cycling was used for the exercise bout and predominantly involves the lower limbs, it is possible that upper limb muscle activity, potentially via the gripping of the cycle ergometer handle bars, occurred during the biking session and influenced the response to the subsequent PAS session. Nevertheless, the accumulating evidence for aerobic exercise influences on neurochemicals (6, 10, 62) and intracortical networks (52, 54) seem more likely candidates for the observed effects.

#### *A Single Bout of Aerobic Exercise Promotes Implicit Sequence-Specific Motor Learning*

Participants demonstrated implicit sequence-specific learning of the temporal element of the motor task when practice was preceded by high-intensity aerobic exercise but not rest. Implicit learning of the spatial component of the task was similarly impacted by rest and exercise. Thus our findings show that, compared with a period of rest, a single bout of aerobic exercise preceding motor task practice specifically promoted the learning of the temporal element of an implicit motor sequence. The lack of implicit learning of the temporal component of the task under the rest condition was not wholly unexpected. We attempted to minimize participants' exposure to the task to reduce any potential carryover effects between the conditions. As implicit learning typically requires relatively high volumes of practice (25, 55), it seems that the volume of practice was not sufficient for implicit learning of the temporal element of the task under the rest condition but that the priming effect of exercise reduced the amount of practice necessary for formation of the implicit memory. Although implicit motor learning is supported by a distributed network of brain regions (16, 18, 20, 22), previous work has demonstrated a distinct role for the cerebellum in improvements in temporal precision during implicit motor learning (3). Thus our finding that

aerobic exercise specifically influenced CT task improvements in temporal precision suggests that cerebellar function may be impacted by a single bout of aerobic exercise. Additionally, previous work demonstrated that PAS delivered with a 25-ms interstimulus interval, as was employed in the present study, is influenced by modulation of cerebellar activity via transcranial direct current stimulation (19). As such, it is possible that an aerobic exercise effect on cerebellar function may also have contributed to our concurrent finding that aerobic exercise facilitated the response of the motor cortex to PAS. Although our findings point toward a cerebellar role, it is unlikely that aerobic exercise exclusively affects the cerebellum. For instance, aerobic exercise can impact gene expression of multiple proteins involved in neuroplasticity (59) across multiple central nervous system regions (17, 38). Moreover, as cerebellar involvement was not directly evaluated in the present study, we cannot conclusively ascertain the extent of its involvement in the observed effects.

Previously, aerobic exercise before task practice impacted motor performance at retention but not over practice blocks (i.e., acquisition) (46). This finding contrasts previous data demonstrating improved performance on various cognitive tasks immediately following a bout of aerobic exercise (29). For example, the acquisition rate of novel words during an associative vocabulary learning task was immediately increased by 20% following high-intensity interval running compared with rest (62). Roig and colleagues (46) suggested that the lack of effect of aerobic exercise on short-term motor skill acquisition may have been attributable to fatigue from the aerobic exercise bout that masked improvements in tracking accuracy during the practice session. Our results demonstrate an effect of the aerobic exercise bout on acquisition of temporal precision over acquisition (i.e., early to late practice) and retention. As we utilized an aerobic exercise bout of similar structure and intensity to that employed by Roig et al. (46), our separation of the spatial and temporal components of implicit sequence-specific learning likely allowed us to more sensitively detect the impact of the aerobic exercise bout on skill acquisition.

#### *Systemic BDNF Is Increased by a Single Bout of Aerobic Exercise*

BDNF is a member of the neurotrophin family of proteins, which are heavily involved in neuroprotection, neurogenesis, and neuroplasticity (1, 44). Animal research has demonstrated a crucial role of BDNF in LTP and motor learning (24, 27, 60), as well as increased BDNF gene expression throughout the central nervous system induced by aerobic exercise (17, 38, 59). Consistent with the majority of previous research in humans (28), we found a marked increase in systemic BDNF after the high-intensity aerobic exercise bout; however, the increase in serum BDNF was not associated with the effects of aerobic exercise on neuroplasticity and motor learning. Although animal work suggests that systemic BDNF levels correlate with centrally derived measures (39, 50), BDNF is released in an activity-dependent manner in the spinal cord and periphery (17), and whether it readily crosses the blood-brain barrier in humans remains a point of contention (37). Thus the lack of relationships in our data may relate to differences in BDNF levels between the periphery and the brain. Addi-

tionally, upregulation of other neurotrophic factors and catecholamines (6, 10, 62) and the presence of genetic variants that impact such neurochemicals (23, 40) could also mask the presence of any potential relationships. Although elevated levels of BDNF throughout the brain following exercise could plausibly facilitate the LTP-like processes involved in PAS and motor learning, our inability to measure centrally derived BDNF in humans limits our capacity to speculate further on such effects.

Our results also showed no relationship between the effects of aerobic exercise on LTP-like neuroplasticity and implicit motor learning. This finding may point to more complex, and potentially global, actions of aerobic exercise on the brain. For example, our measure of neuroplastic response was obtained from motor cortex, but the specificity of our behavioral results to changes in temporal lag indicated a potential influence of aerobic exercise on the cerebellum (3). Although the PAS effects on motor cortex may have involved cerebellar circuitry (19), a more direct measure of aerobic exercise impact on plasticity in the cerebellum may have correlated more strongly with the behavioral outcome. Additionally, although the repeated-measures design for the motor learning task was designed to balance the order of sessions across the group, it may have impacted the magnitude of the effects observed within individuals and affected our ability to detect relationships. Despite the absence of significant correlations within our results, the concurrent finding of increased LTP-like neuroplasticity, motor learning, and systemic BDNF following a single bout of aerobic exercise suggests a likely interplay between these effects.

#### *Conclusions*

In the present study, we discovered that a single bout of high-intensity aerobic exercise facilitated LTP-like responses evoked by excitatory PAS and promoted sequence-specific implicit motor learning specifically associated with improvements in temporal precision. These effects were not related to aerobic exercise-induced increases in systemic BDNF or to each other. Our findings have implications for motor rehabilitation strategies for individuals with neurological injury, such as stroke. As long-term aerobic exercise programs are increasingly prescribed for secondary prevention following stroke (31), the “priming” effects of aerobic exercise on neuroplasticity may be exploited through the strategic pairing of aerobic exercise bouts with motor rehabilitation training. Additional research into underlying mechanisms, as well as how characteristics of the aerobic exercise bout (i.e., intensity, mode, duration) influence these effects, will be important for the optimization of exercise strategies to enhance motor skill learning.

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## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

## AUTHOR CONTRIBUTIONS

Author contributions: C.S.M., K.L.C., C.J.R., and L.A.B. conception and design of research; C.S.M. and N.J.S. performed experiments; C.S.M. analyzed data; C.S.M., N.J.S., K.L.C., C.J.R., and L.A.B. interpreted results of experiments; C.S.M. prepared figures; C.S.M. drafted manuscript; C.S.M., N.J.S., K.L.C., C.J.R., and L.A.B. edited and revised manuscript; C.S.M., N.J.S., K.L.C., C.J.R., and L.A.B. approved final version of manuscript.

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