Acute Aerobic Exercise Modulates Primary Motor Cortex Inhibition

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Abstract

Aerobic exercise can enhance neuroplasticity although presently the neural mechanisms underpinning these benefits remain unclear. One possible mechanism is through effects on primary motor cortex (M1) function via down-regulation of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The aim of the present study was to examine how corticomotor excitability (CME) and M1 intracortical inhibition are modulated in response to a single bout of moderate intensity aerobic exercise. Ten healthy right-handed adults were participants. Single- and paired-pulse transcranial magnetic stimulation (TMS) were applied over left M1 to obtain motor evoked potentials in the right *flexor pollicis brevis* (FPB). We examined CME, short- and long-interval intracortical inhibition (SICI, LICI), and late cortical disinhibition (LCD), before and after acute aerobic exercise (exercise session) or an equivalent duration without exercise (control session). Aerobic exercise was performed on a cycle ergometer for 30 minutes at a workload equivalent to 60% of maximal cardiorespiratory fitness (VO_2 peak; heart rate reserve = 75 ± 3%, perceived exertion = 13.5 ± 0.7). LICI was reduced at 10 (52 ± 17%, P = 0.03) and 20 minutes (27 ± 8%, P = 0.03) post-exercise compared to baseline (13 ± 4%). No significant changes in CME, SICI or LCD were observed. The present study shows that $GABA_B$-mediated intracortical inhibition may be down-regulated after acute aerobic exercise. The potential effects this may have on M1 plasticity remain to be determined.

Introduction

Aerobic exercise exerts a number of positive effects on brain function (Klintsova et al. 2004; Swain et al. 2003; Xiong et al. 2009). Habitual exercise appears to enhance cognitive behaviours which are dependent on underlying neuroplastic mechanisms within the cortex (Cotman and Berchtold 2002). The positive effects of exercise extend beyond purely cognitive executive-functions including working memory and attention (Kramer and Erickson 2007) to the motor domain (Roig et al. 2012). There is accumulating evidence for enhanced neuroplastic responses within the primary motor cortex (M1) following both acute (McDonnell et al. 2013) and chronic (Cirillo et al. 2009) participation in aerobic exercise. A window of enhanced neuroplasticity following exercise could explain exercise associated enhancements in cognitive and motor functions.

Transcranial magnetic stimulation (TMS) protocols have been used to assess how aerobic exercise influences plasticity in M1. For example, Cirillo et al. (2009) found that regular aerobic exercisers had an increased response to paired associative stimulation (PAS), compared with sedentary individuals. The authors concluded that the capacity to induce LTP-like plasticity in M1 was significantly greater in physically active individuals. An augmentation of PAS effects were also observed in response to acute aerobic exercise (Mang et al. 2014; Singh et al. 2014b). Similarly, McDonnell et al. (2013) showed an enhanced neuroplastic response to continuous theta-burst stimulation (cTBS) following a single bout of aerobic exercise. In some individuals M1 excitability is reduced by cTBS, mediated by LTD-like mechanisms (Hamada et al. 2013; Huang et al. 2005). The above studies indicate that aerobic exercise may increase the capability for the induction of LTP- or LTD-like plasticity in human M1.

Paired-pulse TMS can be used to investigate intracortical inhibitory networks within M1. The primary inhibitory neurotransmitter within M1 is gamma-aminobutyric acid (GABA)

which has a distinct affinity for two receptor sub-types, $GABA_A$ and $GABA_B$ (Bachtiar and Stagg 2014). Short interval intracortical inhibition (SICI) is a measure of postsynaptic $GABA_A$ activity and is examined using a sub-threshold conditioning stimulus preceding a supra-threshold test stimulus at short (1-5 ms) interstimulus intervals (ISIs) (Kujirai et al. 1993). Long-interval intracortical inhibition (LICI) is a measure of postsynaptic $GABA_B$ activity that occurs when two supra-threshold stimuli are delivered at longer ISIs between 50-200 ms (McDonnell et al. 2006; Valls-Sole et al. 1992). Recently, a period of late cortical disinhibition (LCD) has been identified in human M1 (Cash et al. 2010). This phenomenon is thought to arise due to activation of presynaptic $GABA_B$ receptors, limiting further GABA release onto postsynaptic GABA receptors. In summary, the use of sub- or supra-threshold conditioning stimuli permit the investigation of distinct $GABA_A$- and $GABA_B$-mediated inhibition respectively.

Modulation of GABA is a candidate mechanism surrounding enhanced cortical neuroplasticity following aerobic exercise. For example, there can be reduced intracortical inhibition within M1 of a non-exercised upper limb muscle following an acute bout (20-30 min) of moderate intensity aerobic exercise (Singh et al. 2014a; Smith et al. 2014). To date, studies have been primarily confined to examining $GABA_A$-mediated SICI (Singh et al. 2014a; Smith et al. 2014) although one study investigated the effect of aerobic exercise on $GABA_B$-mediated LICI, but their results were inconclusive (Singh et al. 2014a). Therefore, it remains unclear whether reduced $GABA_A$-mediated SICI after aerobic exercise extends to pre- and postsynaptic $GABA_B$-mediated inhibition, and the extent of temporal specificity of disinhibition. Regardless of the exact GABA receptor implicated, a release of inhibition may provide a more favourable environment for the induction of neuroplasticity after exercise.

The aim of the present study was to investigate how a single bout of moderate intensity aerobic exercise influences intracortical inhibition in healthy adults. Paired-pulse TMS

protocols were used to assess corticomotor excitability (CME), SICI, LICI and LCD before and after exercise, or an equivalent duration (no-exercise) control condition. We hypothesised that aerobic exercise would reduce SICI and LICI. We also sought to determine whether aerobic exercise was related to an enhancement of LCD.

Methods

Participants

Ten healthy young adults (3 females, mean age 23 ± 2 years, range 18 - 33 years) with no history of neurological illness participated in this study. Participants were screened for contraindications to TMS by a neurologist, and for exercise (Physical Activity Readiness Questionnaire, PAR-Q) (Thomas et al. 1992). All participants were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield 1971), with a mean Laterality Quotient of 87 ± 4 (range 63 - 100). Self-reported physical activity levels were obtained using the long form of the New Zealand Physical Activity Questionnaire (NZ-PAQ). Each participant provided written informed consent and the study was approved by the University of Auckland Human Participants Research Ethics Committee.

Experimental Design

Participants completed three experimental sessions. The first session determined the cardiorespiratory fitness of each participant via an incremental aerobic capacity test (VO_2 peak test). For the second and third sessions, participants were pseudorandomly allocated (www.rando.la) to either 30 minutes of moderate intensity exercise (experimental intervention) or no exercise (control intervention), in a repeated measures crossover design. Session order was counterbalanced, with participant characteristics matched for age, gender, and VO_2 peak

to minimise variance between those who exercised in the first TMS session and those who exercised in the second TMS session. CME and intracortical inhibition were investigated before and after (up to 1 hour) each intervention using TMS.

Aerobic Capacity Testing

Approximately 24 hours before the first TMS session, participants underwent an cardiorespiratory fitness test on an electronically-braked bicycle ergometer (Velotron, Racermate, Seattle, WA). The protocol was used to elicit a maximal rate of oxygen consumption and to determine the relationship between submaximal workload (W) and oxygen consumption (VO_2). A starting workload was estimated from the NZ-PAQ self-reported levels of physical activity (range 60-120 W). Following a 1 minute warm-up, the workload was increased incrementally by 15 W every minute until voluntary exhaustion (mean test duration 11min 5s ± 30s, range 8min 42s – 14min 0s). Heart rate (HR) and Borg's 6 – 20 rating of perceived exertion (PE) (Borg 1970) were recorded every minute. Pulmonary ventilation was measured with a respiratory flow head (GAK-801 Hans Rudolph, Shawnee, KS, USA) and gas composition was analysed using an infrared CO_2 sensor and paramagnetic O_2 detector (MOXUS Modular System, AEI Technologies, Twecula, CA). Metabolic data were captured using a Powerlab 16/35 and LabChart 7 data acquisition system (ADInstruments, Dunedin, New Zealand) configured to provide breath-by-breath analysis. VO_2 peak was defined as the maximum oxygen consumption rate identifiable in a 10 second averaged epoch. Five minutes after the VO_2 peak test, cycling resumed at an estimated submaximal intensity (60% VO_2 peak) in order to confirm that the interpolated workload elicited the required VO_2, HR and PE values.

Electromyography

Surface electromyography (EMG) was recorded from the *flexor pollicis brevis* (FPB) muscle of the dominant right hand using 10 mm-diameter Ag-AgCl recording electrodes (Ambu, Ballerup, Denmark). The electrodes were arranged in a belly-tendon montage with a ground (20 mm-diameter surface electrode; 3M, Canada Health Care) positioned on the dorsum of the hand. EMG signals were amplified (Grass P511AC, Grass Instrument Division, West Warwick, RD) with a gain of 1000, band-pass filtered (30-1000 Hz) and sampled at 2 kHz using a 16-bit A/D acquisition system (National Instruments, Austin, TX) and recorded onto a computer for offline analysis using LabVIEW (National Instruments, Austin, TX) software.

Transcranial Magnetic Stimulation

Participants sat in a chair with their dominant right hand and forearm strapped to a moulded plastic cast and resting on a table top. Motion of the fingers and wrist were restricted but the thumb was unconstrained. Single- and paired-pulse TMS was delivered to left M1 using two MagStim 200 magnetic stimulators connected to a BiStim unit (MagStim, Dyfed, UK) and a 70 mm diameter figure-of-eight coil. The coil was held tangentially to the scalp, with the handle posterior approximately 45° to the mid-sagittal line, to induce posterior-anterior current flow in the brain (Sakai et al. 1997). The optimal site to elicit consistent motor evoked potentials (MEPs) in the resting FPB muscle was marked on the scalp. TMS was delivered at 0.2 Hz for all conditions and optimal coil position was continually monitored throughout the experiment.

Active motor threshold (AMT) was defined as the minimum stimulus intensity required to elicit a MEP of at least 100 μV in amplitude, in four out of eight trials (Eichhammer et al. 2007), with FPB voluntarily activated to approximately 10% of the participant's perceived

maximum voluntary contraction (MVC). The stimulus intensity was altered in 1% increments of maximum stimulator output (MSO) throughout this process.

Measurement of cortical silent period (SP) duration was made during a low-level contraction of FPB (10% MVC). Stimulation intensity was adjusted to elicit a SP of 175 ms (TS_{175}). In the first study to identify LCD (Cash et al. 2010), the ISI for optimal LCD was strongly correlated with the SP duration elicited by the CS. Therefore, we tailored the CS for each individual to elicit a target SP duration of 175 ms to set our ISIs for LCD at 175 ms and 200 ms. A total of 16 TMS pulses were delivered using TS_{175}, with participants instructed to maintain their contraction until given the instruction to relax.

SICI was assessed using a paired-pulse TMS protocol consisting of a subthreshold conditioning stimulus (CS) that preceded a suprathreshold TS by 1 ms ($SICI_{1ms}$) and 2.5 ms ($SICI_{2.5ms}$) (Roshan et al. 2003). The TS intensity was set to elicit a MEP amplitude of approximately 1 mV (TS_{1mV}) in the resting FPB, whereas the intensity of the CS was initially set at 80% of AMT and adjusted, if required, to produce at least 50% inhibition (CS_{50}) of the TS response for $SICI_{2.5ms}$. For both $SICI_{1ms}$ and $SICI_{2.5ms}$, 12 conditioned (C) and 6 non-conditioned (NC) stimuli were delivered in a randomised order throughout the block. NC MEPs were pooled across the two blocks.

LICI and LCD were assessed using a paired-pulse TMS protocol performed at rest. Both TMS pulses were set to TS_{175} and ISIs of 125 ms, 175 ms, and 200 ms were investigated. Each data block consisted of 16 trials for each of the three ISIs with the order of presentation randomised throughout the trials (48 trials in total).

Intervention

For both exercise and control interventions, participants were seated on a cycle ergometer (Monark, Dalarna, Sweden) for a period of 30 minutes. It is unlikely that fatigue in

the lower-limb muscles from the VO_2 peak test was present in those individuals who performed the exercise intervention in the second session (Bazelmans et al. 2005). HR was measured during both sessions along with EMG activity to ensure the FPB muscle remained inactive. A raised table positioned over the cycle ergometer ensured both upper limbs remained in the same posture as during baseline measures. For the exercise session, each participant cycled at a workload corresponding to 60% of their peak oxygen uptake. As per the American College of Sports Medicine guidelines, an intensity of 60% VO_2 peak corresponds to a moderate exercise intensity, and is recommended for most healthy adults (Garber et al. 2011). PE was monitored and water was offered every 5 minutes. For the control session, participants sat stationary on the cycle ergometer. Following each intervention, each participant sat quietly for 10 minutes. Post measurements of SP duration, LICI/LCD and SICI were repeated 5 times, separated by approximately 10 minutes.

Data Analysis

Group means were calculated for physiological measures obtained both during the VO_2 testing session and during the 30 minute intervention period (exercise, control). These included; VO_2 peak, resting HR and mean HR30min. Age-predicted max HR (220 – age) and resting HR (attained during the control intervention) were used to calculate each participant's heart rate reserve (HRR; age-predicted max HR – resting HR), which is commonly used to establish sub-maximal exercise intensities. The intensity of the exercise during the 30 minute intervention was expressed as a percentage of HRR using: ((Mean HR30min – Resting HR) / HRR).

EMG activity collected online during both the 30 minute experimental and control interventions was analysed to find the root mean squared (rms) EMG activity for the FPB muscle. Pre-trigger rmsEMG activity was determined, for all paired-pulse TMS trials, within a

window spanning 55 to 5 ms before the first stimulus. The threshold for pre-trigger rms activity was 10 μV and trials exceeding this level of background EMG were discarded.

Semi-automated methods were used to measure SP duration, determined by the resumption of EMG activity in the FPB muscle to a level equal to or above pre-trigger rmsEMG. Trials in which participants were not able to maintain the contraction through the perturbation of the stimulus were excluded. $SICI_{1ms}$ and $SICI_{2.5ms}$ was calculated by expressing the C MEP amplitude as a percentage of the NC MEP amplitude (C/NC × 100), for each respective time point. Because two ISIs (175 and 200 ms) were used to assess LCD, the ISI eliciting optimal conditioned responses at baseline, i.e. larger conditioned MEPs, was analysed for each participant and kept constant for each post time point. LICI and LCD were calculated by expressing the mean conditioned MEP amplitude as a percentage of the mean NC MEP amplitude (C/NC × 100), for each respective ISI (LICI and optimal LCD). The MEP produced by the preceding suprathreshold CS was used to determine the NC MEP amplitude. In addition to the measures of inhibition, peak-to-peak NC MEP amplitudes from the SICI and LICI/LCD protocols were used to index CME.

Statistical Analysis

Normality was tested using the Shapiro-Wilk's test. Each dependent variable was analysed with a 2 SESSION (Rest, Exercise) x 6 TIME (B, P10, P20, P30, P40, P50) repeated measures analysis of variance (rmANOVA) with $\alpha = .05$. The data from one participant were excluded for SICI analysis because there was no measurable inhibition at baseline. For all rmANOVA where assumptions of sphericity were violated, the critical F value was adjusted by the Greenhouse-Geisser Epsilon value from the Mauchly test of sphericity. Post-hoc analyses were performed with paired t-tests, Bonferroni corrected for multiple comparisons (Rom 1990).

Paired t-tests were used for manipulation checks of exercise intensity (%HRR, PE), rmsEMG in the FPB muscle during lower-limb exercise, and TMS stimulation parameters (AMT, CS_{50}, TS_{1mV}). All group data are presented as mean ± SEM in the text.

Results

Participants completed all three experimental sessions, with no adverse effects reported during either the exercise or TMS components of the study. Participant characteristics and VO_2 session variables are reported in Table 1. The group mean VO_2 peak was 4.56 ± 0.29 L/min with participants reaching an average max power output of 264 ± 17 W. During the additional 15 min of submaximal exercise, 60% VO_2 peak corresponded to an intensity of 75 ± 3 % HRR. This was no different to the intensity achieved during the exercise intervention of the TMS session (73 ± 5 % HRR, $t_9 = -1.22$, $P = 0.25$). There was no difference in PE reported by the participants during the VO_2 submaximal exercise bout (13.5 ± 0.7) and the exercise intervention (13.5 ± 0.4; $t_9 = 0.22$, $P = 0.83$). No difference in rmsEMG collected online from the FPB muscle during the exercise (6.5 ± 0.8 μV) and control (6.7 ± 0.9 μV) interventions was observed ($t_9 = 0.16$, $P = 0.87$).

There were no differences in AMT or CS_{50} and TS_{1mV} intensities between TMS sessions (all $P > 0.35$). Analysis of NC MEP amplitude obtained from the SICI protocol revealed no main effect of SESSION ($F_{1, 8} = 0.003$, $P = 0.96$), TIME ($F_{1.6, 12.8} = 0.686$, $P = 0.49$), or TIME × SESSION interaction ($F_{5, 40} = 1.712$, $P = 0.15$; Baseline exercise session 1.08 ± 0.13 mV, Baseline control session 1.13 ± 0.21 mV). Similarly, analysis of NC MEP amplitude obtained from the LICI/LCD protocol revealed no main effect of SESSION ($F_{1, 9} < 0.001$, $P = 0.99$), TIME ($F_{5, 45} = 0.446$, $P = 0.81$) or TIME × SESSION interaction ($F_{2.7, 24.1} = 2.180$, $P = 0.12$; Baseline exercise session 0.81 ± 0.16 mV, Baseline control session 1.04 ± 0.25 mV).

For SP duration (Figure 1a), there was a trend for the main effect of TIME ($F_{2.1, 19.0}$ = 3.260, P = 0.06), no main effect of SESSION ($F_{1, 9}$ = 0.104, P = 0.76) and no TIME × SESSION interaction ($F_{5, 45}$ = 1.695, P = 0.16). Analysis of pre-trigger rmsEMG revealed no main effect of TIME ($F_{1.8, 16.5}$ = 2.387, P = 0.13), SESSION ($F_{1, 9}$ = 0.537, P = 0.48) or a TIME × SESSION interaction ($F_{1.6, 14.8}$ = 0.270, P = 0.73). There was no difference in TS_{175} between TMS sessions (Rest: 62 ± 4 %MSO, Ex: 60 ± 3 %MSO, t_9 = -0.64, P = 0.54).

SICI results are shown in Figures 1b ($SICI_{1ms}$) and 1c ($SICI_{2.5ms}$). For $SICI_{1ms}$ there was a trend of TIME ($F_{2.6, 20.4}$ = 2.767, P = 0.08), but not SESSION ($F_{1, 8}$ = 0.853, P = 0.38) or a TIME × SESSION interaction ($F_{2.7, 21.4}$ = 1.149, P = 0.35). For $SICI_{2.5ms}$ there was no main effect of SESSION ($F_{1, 8}$ = 0.026, P = 0.88), TIME ($F_{5, 40}$ = 1.712, P = 0.15) or TIME × SESSION interaction ($F_{1.9, 15.3}$ = 0.368, P = 0.69).

LICI data are presented in Figure 1d. There was no main effect of SESSION ($F_{1, 9}$ = 1.512, P = 0.25), but there was a main effect of TIME ($F_{2.2, 19.9}$ = 4.766, P = 0.02), and a TIME × SESSION interaction ($F_{5, 45}$ = 2.587, P = 0.04). Bonferroni corrected post-hoc comparisons revealed that LICI was reduced in the exercise session at P10 (52 ± 17%, t_9 = -2.56, P = 0.03) and P20 (27 ± 8%, t_9 = -2.60, P = 0.03) compared to baseline (13 ± 4%). For LCD, there was no main effect of SESSION ($F_{1, 9}$ = 3.153, P = 0.11), TIME ($F_{5, 45}$ = 0.779, P = 0.57) or TIME × SESSION interaction ($F_{5, 45}$ = 0.905, P = 0.49). Furthermore, baseline assessment of LCD revealed that disinihibtion was not present for both exercise (105 ± 24%) and control (122 ± 32%) sessions.

Discussion

The results of the present study support the hypothesis that a single-bout of moderate intensity aerobic exercise modulates M1 inhibition. A release of GABA-mediated inhibition is necessary for the facilitation of neuroplasticity within M1 and a reduction in $GABA_B$-mediated

LICI was observed in this study. Reduced LICI may be a candidate mechanism contributing to enhanced neuroplasticity seen after both acute (McDonnell et al. 2013; Singh et al. 2014b) and chronic exposure to aerobic exercise (Cirillo et al. 2009).

An acute bout of moderate intensity aerobic exercise did not modulate CME obtained in a non-exercised intrinsic hand muscle. This finding is consistent with previous studies (McDonnell et al. 2013; Sidhu et al. 2012; Singh et al. 2014a; Smith et al. 2014). We expand on previous studies by quantitatively assessing the aerobic fitness of each individual, which was then tailored to achieve an exercise intervention of moderate intensity. This tailored approach may be advantageous for implementing exercise as an adjunct to enhance motor recovery following neurological injury. To the best of our knowledge, this study was also the first to record EMG activity in the non-exercised TMS target muscle (FPB) during the intervention, showing that the target muscle remained at rest throughout the exercise period. Together the results from our study and others show that acute (20-30 min) aerobic exercise has no modulating effect on CME in non-exercised muscles.

Following a single bout of aerobic exercise SICI may be reduced in M1 representations of both exercised (Yamaguchi et al., 2012) and non-exercised muscles (Singh et al. 2014a; Smith et al. 2014; Yamaguchi et al. 2012). This was not observed in the current study. Differences in stimulation parameters and experimental procedures between studies may explain the contrasting results. We specifically chose to investigate exercise associated changes in $SICI_{1ms}$ and $SICI_{2.5ms}$ as peak inhibition occurs at these ISIs (Fisher et al. 2002; Roshan et al. 2003). It has been postulated that two distinct cortical mechanisms give rise to each inhibition peak, with extrasynaptic and synaptic $GABA_A$ activity markers of $SICI_{1ms}$ and $SICI_{2.5ms}$ respectively (Stagg et al. 2011b). The present study is the first to investigate exercise associated changes in $SICI_{1ms}$, and no effect of exercise was detected. In contrast to our findings a previous investigation found decreased $SICI_{2.5ms}$ after exercise (Singh et al. 2014a). Further, in

an intrinsic hand muscle, voluntary activity prior to assessment of SICI at rest in the same muscle has been associated with increased inhibition for a period of 20 min (Teo et al. 2012). A possible limitation of the present study was that measures of SP duration were taken prior to measures of SICI during the pre- and post-intervention blocks, requiring multiple isometric contractions of FPB muscle only minutes before SICI measures were obtained. This may have masked exercise associated effects, and may explain why there was no reduction in SICI post-exercise as demonstrated in some previous studies.

LICI decreased after an acute bout of aerobic exercise. In contrast we did not observe an effect on SP duration. Both LICI and SP duration are considered markers of $GABA_B$-mediated inhibition. However, they are not identical processes. LICI reflects CME in response to a second TMS pulse, whereas SP duration reflects the interruption of voluntary activation of the corticomotor pathway (McDonnell et al. 2006). Furthermore, administration of baclofen, a $GABA_B$ agonist, increases LICI with no specific effect on SP duration (McDonnell et al. 2006; Ziemann et al. 1996). The apparent dissociation between LICI and SP duration may extend to aerobic exercise effects. Decreased LICI is in contrast to a previous study (Singh et al. 2014a) that assessed LICI immediately and 30 min after exercise. In their study, Singh et al. (2014a) observed no change in LICI immediately after exercise and a trend for reduced LICI at 30 min. We found that LICI was reduced at 10 and 20 min post exercise. Interestingly, post measurements made by Singh et al. (2014a) fall either side of these time points. The time window in which measurements after exercise were obtained could account for the contrasting results. Singh et al. (2014a) also genotyped participants for the BDNF polymorphism (valine-to-methionine substitution at codon 66). Methionine allele (MET) carriers show decreased activity-dependent BDNF release (Egan et al. 2003). Interestingly, the trend for reduced LICI at 30 min post exercise was not present in MET carriers (Singh et al. 2014a). While the mechanisms surrounding the exercise associated modulation of LICI seen in our study are

unclear, an exercise-induced increase in BDNF release may be one of the mechanisms responsible.

Reduced LICI after exercise may have practical implications. A release of GABAergic inhibition is necessary for the induction of LTP-like plasticity and it is understood that there are decreased GABA concentrations within primary sensorimotor cortex during learning of a motor task (Floyer-Lea et al. 2006; Stagg et al. 2011a). In a previous study, modulation of LICI was associated with an intervention that led to enhanced motor skill learning (Byblow et al. 2012). An exercise associated release in $GABA_B$-mediated LICI may enhance early acquisition and consolidation of skills, leading to improved motor memory and performance. In animal models, modulation of GABAergic signalling is necessary for functional recovery after stroke (Clarkson et al. 2010) and a prominent role for a reduction in SICI in facilitating motor recovery post-stroke is also found in human (Blicher et al. 2009; Hummel et al. 2009; Stinear et al. 2008; Stinear et al. 2014). Disinhibition effects may extend to a more globalised reduction of inhibitory activity in measures of LICI (Swayne et al. 2008). Our findings present the potential for aerobic exercise to be used as a priming technique for both motor learning and motor recovery after stroke. Aerobic exercise may provide a more favourable environment for cortical reorganisation through a reduction in GABAergic inhibition, leading to the facilitation of skill acquisition and motor recovery.

To our knowledge, this is the first study to investigate whether an acute bout of exercise influences LCD. The period of LCD is thought to represent a reduction in GABA release due to presynaptic activation of $GABA_B$ receptors (Cash et al. 2010), whereas LICI is mediated by postsynaptic activation of $GABA_B$ receptors (McDonnell et al. 2006). Unfortunately, we did not observe a consistent period of LCD as seen in previous studies (Cash et al. 2010; Cash et al. 2011), perhaps because LCD is more prominent during voluntary activation than at rest (Caux-Dedeystere et al. 2015; Caux-Dedeystere et al. 2014). To maximize the possibility of

detecting the presence of LCD future studies may choose to voluntarily contract the muscle of interest. Currently it remains unclear whether the exercise-related modulation of postsynaptic $GABA_B$ activity reflected in our LICI data extends to presynaptic $GABA_B$ activity.

In summary, an acute bout of aerobic exercise reduced inhibition within human M1 via $GABA_B$-mediated LICI measures obtained in a non-exercised intrinsic hand muscle. It is becoming increasingly evident that GABA-mediated inhibition is transiently reduced post-exercise. Future studies should investigate how generalizable this is across exercise intensities, durations and muscle representations.

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Disclosures

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

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Tables

Table 1. Participant characteristics and VO_2 session variables

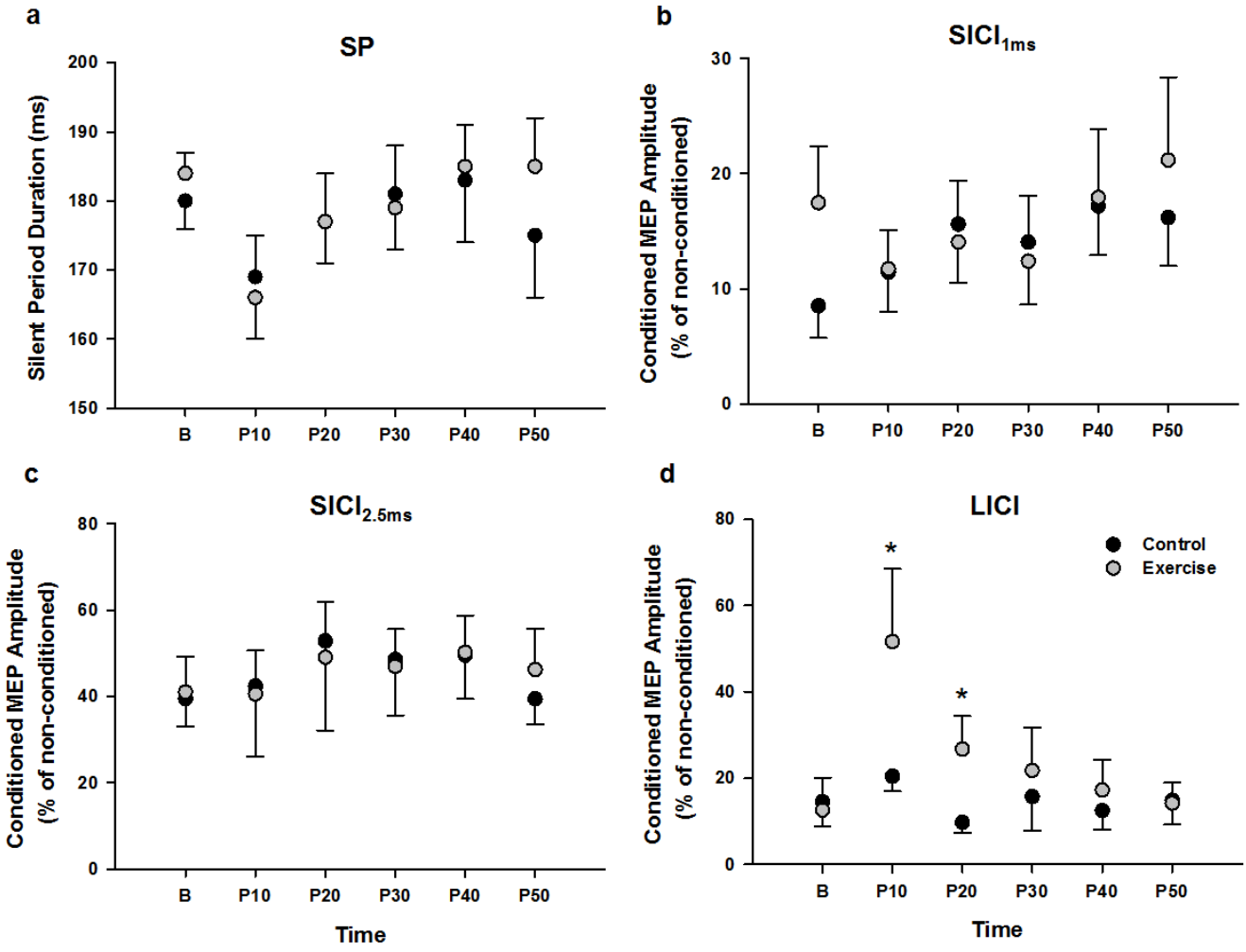
Participant	Age (yrs)	Gender	LQ	Rest HR (bpm)	HRR (bpm)	PA (Met-min/wk)	VO_2 peak (L/min)	Max Power (W)
1	24	F	92	81	115	4040	4.41	265
2	23	F	88	65	132	2040	3.31	200
3	33	M	75	71	116	3960	4.45	235
4	20	F	63	68	132	4560	3.43	230
5	21	M	88	52	147	5360	5.00	280
6	21	M	100	70	129	1200	5.02	280
7	30	M	83	71	119	1620	3.82	220
8	21	M	100	48	151	19080	5.75	270
9	18	M	100	61	141	1000	4.42	265
10	20	M	78	70	130	3600	6.00	395
Mean	**23**	**-**	**87**	**66**	**131**	**4646**	**4.56**	**264**
SEM	2	-	4	3	4	1673	0.29	17

Note: *HR* – heart rate, *HRR* – heart rate reserve, *LQ* – laterality quotient assessed by the Edinburgh Handeness Inventory, PA – self-report physical activity levels from the New Zealand Physical Activty Questionnaire

Figure Captions

Figure 1 Intracortical inhibition. (**a**) Cortical silent period duration, (**b**) short-interval intracortical inhibition (SICI) at 1 ms, (**c**) SICI at 2.5ms and (**d**) long-interval intracortical inhibition (LICI) recorded from right flexor pollicis brevis at baseline (B) and 10 - 50 min after (P) acute moderate intensity lower-limb aerobic exercise versus control. Reductions in LICI were observed at P10 and P20 in the exercise session compared to B. *$P < 0.05$. Symbols are group means ± SEM.

Figure 1


a
SP
Silent Period Duration (ms)
200
190
180
170
160
150
B
P10
P20
P30
P40
P50
b
SICI1ms
Conditioned MEP Amplitude (% of non-conditioned)
30
20
10
0
c
SICI2.5ms
80
60
40
20
0
Time
d
LICI
Control
Exercise
*
*