Acute high-intensity and moderate-intensity interval exercise do not change corticospinal excitability in low fit, young adults

Jenin El-Sayes, Claudia V. Turco, Lauren E. Skelly, Mitchell B. Locke, Martin J. Gibala, Aimee J. Nelson*

Department of Kinesiology, McMaster University, Hamilton, Canada

Abstract

Previous research has demonstrated a lack of neuroplasticity induced by acute exercise in low fit individuals, but the influence of exercise intensity is unclear. In the present study, we assessed the effect of acute high-intensity (HI) or moderate-intensity (MOD) interval exercise on neuroplasticity in individuals with low fitness, as determined by a peak oxygen uptake (VO\textsubscript{2peak}) test (n = 19). Transcranial magnetic stimulation (TMS) was used to assess corticospinal excitability via area under the motor evoked potential (MEP) recruitment curve before and following training. Corticospinal excitability was unchanged after HI and MOD, suggesting no effect of acute exercise on neuroplasticity as measured via TMS in sedentary, young individuals. Repeated bouts of exercise, i.e., physical training, may be required to induce short-term changes in corticospinal excitability in previously sedentary individuals.

Introduction

Transcranial magnetic stimulation (TMS) provides a unique opportunity to non-invasively assess neuroplasticity within the motor system. Single-pulse TMS to the primary motor cortex (M1) can be used to acquire motor-evoked potentials (MEPs), an indicator of corticospinal excitability [1]. One goal of rehabilitation is to alter corticospinal excitability, and this can be measured by changes in the MEP amplitude. Exercise is both cost-effective and can be combined with other rehabilitation protocols to augment the effects of motor re-learning [2]. Numerous studies have used TMS to assess neuroplasticity within the motor system after an acute session of aerobic exercise in healthy individuals (Table 1). These studies have reported either no change [3–7] or an increase [6,8,9] in MEP amplitude following exercise. The discrepancy may relate to either the fitness level of the participants tested, or the intensity of the exercise performed. However, the discrepancy may also relate to the method by which fitness is assessed. For example, the International Physical Activity Questionnaire (IPAQ) is commonly used to assess physical activity and not fitness per se, whereas a peak oxygen uptake (VO\textsubscript{2peak}) test provides an indication of cardiorespiratory fitness. Studies reporting an increase in MEP amplitude after acute exercise were generally performed using highly fit individuals as gauged by a VO\textsubscript{2peak} test [8,9] or in highly active individuals as gauged by the IPAQ [6].
Exercise intensity does not impact neuroplasticity in low fit adults

Table 1. Effects of acute cycling on upper limb neurophysiology.

| Reference            | Population                                                                 | Exercise                          | MEPs                        |
|----------------------|----------------------------------------------------------------------------|-----------------------------------|-----------------------------|
| Singh et al. [4]     | n = 12 (5 females, activity level not reported)                            | MICT (65–70% age-predicted HR\textsubscript{max}) | $\uparrow^*$                   |
| Lulic et al. [6]     | n = 14 active (9 females, IPAQ: 7631 ± 6120) n = 14 sedentary (8 females, IPAQ: 1305 ± 773) | MICT (60% age-predicted HR\textsubscript{max}) | $\uparrow$ in fit group only$^a$ |
| Smith et al. [5]     | n = 9 sedentary (4 females, IPAQ: 1784 ± 361)                             | LICT (40% HRR) M-HICT (80% HRR)   | $\parallel$ following both interventions$^a$ |
| Stavrinos & Coxon [10]| n = 24 sedentary (10 females, IPAQ: 2770 ± 1602)                        | HIIT (90% HRR, 50% HRR)           | $\parallel$                   |
| McDonnell et al. [3] | n = 25 sedentary (16 females, IPAQ: 1630 ± 906)                          | LICT (55–65% age-predicted HR\textsubscript{max}) MICT (75% age-predicted HR\textsubscript{max}) | $\parallel$ following both interventions$^a$ |
| El-Sayes et al. [8]  | n = 34 fit (17 females, VO\textsubscript{2peak}: 46.4 ± 6.6 mL/kg/min)    | MICT (65–70% HR\textsubscript{max}) | $\uparrow^*$                  |
| MacDonald et al. [9] | n = 15 sedentary-fit (8 females, VO\textsubscript{2peak}: 33.7 ± 7.0 mL/kg/min [range of 22.1–48.2]) | LICT (30% HRR) MICT (40–50% HRR) | $\uparrow$ after MICT only$^a$ |
| Neva et al. [7]      | n = 12 active (6 females, IPAQ: 5112 ± 686)                              | MICT (65–70% VO\textsubscript{2peak}) | $\parallel$                   |
| Andrews et al. [11]  | n = 20 sedentary-active (11 females, IPAQ: 4681 ± 2287)                  | MICT (50% HRR) HIIT (90% HRR, 50% HRR) | $\parallel$ following both interventions$^a$ |
| Opie & Semmler [12]  | n = 13 (5 females, activity level not reported)                           | LICT (50% HRR) HIIT (77% HRR, 25% HRR) | $\parallel$ following both interventions$^a$ |

MEPs: motor-evoked potentials; IPAQ: International Physical Activity Questionnaire; VO\textsubscript{2peak}: cardiorespiratory fitness; MICT: moderate-intensity continuous exercise; LICT: low-intensity continuous exercise; HICT: high-intensity continuous exercise; HIIT: high-intensity interval exercise; HR\textsubscript{max}: maximum heart rate; $\downarrow$: reductions; $\parallel$: no change; $\uparrow$: increases; N/A: not applicable.

$^a$indicates results were obtained immediately post-exercise.

$^b$indicates results were obtained 10-15min post-exercise.
recovery periods [23] and is a potent stimulus for increasing BDNF levels [24]. We chose to use a moderate intensity interval exercise rather than the more commonly used continuous exercise in order to isolate the effect of exercise intensity and remove effects due to the inter-vallic structure of the exercise. Further, fluctuations in metabolic stress (i.e. an intermittent pattern of exercise) have been shown to influence acute skeletal muscle responses to exercise, independent of exercise intensity [25]. In addition, a recent editorial called for future research to compare physiological responses to moderate-intensity interval exercise and high-intensity interval exercise to better understand the influence of intensity independent of the exercise stimulus pattern (i.e. intermittent) [26]. It was hypothesized that HI would increase corticospinal excitability compared to MOD in low fit young adults, as higher intensity exercise evokes increased BDNF [16–18,27] and IGF-1 [14] levels more so than moderate-intensity exercise.

Methods

Participants

Nineteen individuals (22.1 ± 2.6 years; 7 females) participated in three sessions, with a minimum of 48 h between each session. Results from Lulic et al. [6] were used to provide an estimate of the required sample size. The reported effect size for finding a change in MEPs was Cohen’s d of 0.5, and assuming a two-tailed alpha of 0.05 and power of 0.8, this yielded a sample size of 22 participants. All individuals reported no history of neurological disease or illness and were right-hand dominant as determined by the modified version of the Edinburgh Handedness Scale [28]. All participants were of low cardiorespiratory fitness, as determined by a VO₂peak test, and classification in the “poor” category as defined by the Canadian Society for Exercise Physiology (below 41.6 ml/kg/min for males and 35.0 ml/kg/min for females) [29]. Participants had an average VO₂peak of 34.1 ± 4.0 ml/kg/min (coefficient of variation is 11.7%), height of 171.5 ± 9.5 cm, and weight of 69.9 ± 12.6 kg. Participants were also screened for contraindications to TMS [30] and exercise, using a Physical Activity Readiness Questionnaire [31]. Participants were asked to refrain from physical activity on the day of each session, and from consuming alcohol or nicotine for 12 h prior to each session. Written informed consent was obtained prior to participation. This study was approved by the McMaster Research Ethics Board and conformed to the Declaration of Helsinki.

Experimental design

VO₂peak was determined during the first session on an electronically braked cycle ergometer (Lode Excalibur Sport V 2.0, Groningen, the Netherlands) and an on-line gas collection system (Moxus modular oxygen uptake system, AEI Technologies, Pittsburg, PA, USA), as previously described [32]. The VO₂peak test began with a warm-up at 50 W for 2 minutes, then the workload was increased by 1 W every 2 seconds until volitional fatigue occurred or until participants could no longer cycle at 60 r.p.m. The VO₂peak corresponded to the highest value achieved over a 30 second period. To determine if a valid maximal effort was achieved during the VO₂peak test, participants were required to meet two out of four of the following criteria: HRmax within 10 bpm of their predicted maximum, respiratory exchange ratio > 1.1, plateau, and/or volitional exhaustion [33]. All participants exerted maximal effort according to these criteria.

Sessions 2 and 3 followed the experimental timeline in Fig 1. Dependent measures were obtained before exercise (T0) and beginning 10 minutes following the end of the exercise intervention (T1). Post-intervention assessments were obtained 10 minutes post-exercise to ensure that heart rate returned to resting levels before data was collected. The order of dependent measure acquisition within each time block was pseudorandomized using the William
Square Counterbalance. Ten participants (3 females, 7 males) underwent HI in session 2 and MOD in session 3 (described below), while nine participants (4 females, 5 males) underwent MOD followed by HI. Physical activity levels were assessed using the International Physical Activity Questionnaire (IPAQ; [34]) on both experimental sessions to ensure similar physical activity levels were maintained throughout the duration of the study.

**Acute exercise interventions**

HI and MOD were performed via lower limb cycling on an electronically braked cycle ergometer (Ergo Race, Kettler, Germany). Both exercise protocols included a 3 minute warm up at 50 W, ten 1 minute bouts interspersed with 1 minute recovery periods, and a 2 minute cool down (Fig 1). The intensity bouts was 80–100% of maximum heart rate ($HR_{max}$) for HI and 60–79% $HR_{max}$ for MOD [35] and participants were instructed to cycle between 80–100 r.p.m. The recovery periods for both interventions involved light cycling at 50 W [36], and participants were instructed to cycle at a self-selected pace. Heart rate was monitored using telemetry (Polar A3, New York, USA) to obtain continuous data for the 25 minute exercise period and the 10 minute rest period following the exercise. Ratings of perceived exertion (RPE) were acquired at the end of each interval during the intervention using the 0–10 Borg scale [37]. Throughout the exercise, electromyography (EMG) activity of the right first dorsal interosseous (FDI) muscle (EMG$_{exercise}$) was recorded to ensure that the FDI muscle was inactive.

**Electromyography recording**

EMG was recorded from the right FDI using surface electrodes (9 mm diameter Ag-AgCl) placed in a belly tendon montage, with a wet ground electrode placed around the forearm. EMG signals were amplified (x1000), bandpass filtered between 20 Hz and 2.5 kHz (Intronix Technologies Corporation Model 2024F with Signal Conditioning; Intronix Technologies Corporation, Bolton, Canada), and digitized at 5 kHz (Power1401, Cambridge Electronic Design, Cambridge, UK). EMG data were collected using Signal software version 6.02 (Cambridge Electronic Design, Cambridge, UK).

**Maximum M-wave (M-Max)**

M-Max was used to normalize MEPs before and after exercise and defined as the maximum response elicited from the right FDI following ulnar nerve stimulation at the wrist. Nerve
stimulation was delivered using a bar electrode (cathode proximal) and a constant current stimulator (Digitimer DS7AH) delivering 200 μs square wave pulses. Stimulation intensity was increased by 1 mA at each trial until the M-wave ceased to increase in 3 consecutive trials. The peak-to-peak amplitude of the M-wave (mV) was defined as M-Max.

Transcranial magnetic stimulation

Single and paired monophasic TMS pulses were delivered using a custom-built 50 mm diameter figure-of-eight branding coil connected to a Magstim Bistim stimulator (Magstim, Whitland, UK). The TMS coil was positioned 45 degrees in relation to the parasagittal plane to induce a posterior-to-anterior current in the cortex. The motor hotspot for the right FDI was determined within the left motor cortex and defined as the location that elicited large and consistent MEPs. The motor hotspot was digitally registered using Brainsight Neuronavigation (Rogue Research, Canada). RMT was defined as the lowest intensity required to evoke a MEP ≥ 50 μV in 5 out of 10 consecutive trials in the relaxed FDI muscle [30]. MEP recruitment curves were obtained from the right FDI muscle at rest by delivering seven TMS pulses at 100–140% RMT in 10% increments in a randomized order (35 pulses total).

Data analyses

All MEP trials were assessed for background muscle activity. Trials were excluded if the EMG activity immediately before the TMS stimulus artifact exceeded 50 μV [38]. The mean peak-to-peak MEP amplitude at each intensity (100–140% RMT) of the recruitment curve was calculated by averaging the MEPs of the seven trials at each intensity. The Area Under the Recruitment Curve (AURC) was obtained by calculating the trapezoidal integration of the recruitment curve (AURC = (\text{MEP}_{100\%} + \text{MEP}_{110\%}) / 2 + (\text{MEP}_{110\%} + \text{MEP}_{120\%}) / 2 + (\text{MEP}_{120\%} + \text{MEP}_{130\%}) / 2), where \text{MEP}_{100\%} is the MEP amplitude at 100% RMT, etc.). AURC was normalized to M-Max (i.e. AURC/M-Max) at T0 and T1 to account for altered electrode conductance that may follow exercise [39].

Group-level analyses included normality testing using the Shapiro-Wilk’s test. Outliers were identified using IBM SPSS Software as data points 3 times above or below the interquartile range. No outliers were observed in the data. AURC at T0 was assessed using a Wilcoxon Signed-Rank to determine if AURC at T0 was different between HI and MOD. Since no baseline difference was observed (i.e. T0 in HI was not different than T0 in MOD), AURC was assessed using a repeated-measures ANOVA with factors INTERVENTION (2 levels: HI, MOD) and TIME (2 levels: T0, T1). HI versus MOD effects on IPAQ, RPE, EMG_exercise, and heart rate were assessed using paired t-tests in cases where data was normally distributed or Wilcoxon Signed-Rank tests in cases where data was not normally distributed. The significance level was set to p ≤ 0.05 and effect sizes were calculated using Hedge’s g.

Results

All participants were classified as low fit with a mean VO\text{2peak} of 34.1 ± 4.0 ml/kg/min (Fig 2). Physical activity levels, assessed via IPAQ, did not differ between the two experimental sessions (HI: 2302.1 ± 2172.3; MOD: 2245.7 ± 2062.5; Wilcoxon: p = 0.65). Exercise details are presented in Table 2. The average HR during the “on” and “off” intervals were significantly different in both the HI (paired t-test, p < 0.001, g = 0.85) and MOD exercises (paired t-test, p < 0.01, g = 0.41). Further, the %HR_max was significantly different between the “on” and “off” intervals for both the HI (paired t-test, p < 0.001, g = 0.86) and MOD exercises (paired t-test, p < 0.01, g = 0.38). The HI protocol was more intense than MOD as demonstrated by higher
heart rate during bouts (HI: 87.1 ± 6.4% HR$_{\text{max}}$; MOD: 70.4 ± 7.0% HR$_{\text{max}}$, paired t-test, p < 0.001, g = 2.44) and the greater RPE (HI: 5.5 ± 1.3; MOD: 3.5 ± 1.7, paired t-test, p < 0.001, g = 1.13).

RMT was not different between T0 and T1 for HI (Wilcoxon: p = 0.74, g = 0.02) or MOD (Wilcoxon: p = 0.27, g = 0.04). To assess corticospinal excitability, MEP recruitment curves were obtained and the AURC was calculated. Neither HI or MOD induced a significant change in AURC (Fig 3A; INTERVENTION$(_{(1,18)}$ = 1.07, p = 0.31, $\eta^2$ = 0.056, TIME$(_{(1,18)}$ = 0.50, p = 0.49, $\eta^2$ = 0.027, INTERVENTION$^*_{(1,18)}$TIME$(_{(1,18)}$ = 0.01, p = 0.92, $\eta^2$ = 0.001) and there were no differences between HI and MOD at T0 (Wilcoxon: p = 0.42, g = 0.23). There was high between-subject variability in AURC, as shown by the coefficient of variation (HI T0: 67.3%, HI T1: 53.0%, MOD T0: 69.7%, MOD T1: 78.5%). Percent change in AUC (i.e. T0 to T1) for HI and MOD were not different (Fig 3B; Wilcoxon: p = 0.66, g = 0.03). Individual data are depicted in Fig 3C showing variable responses in AURC to HI and MOD.

![Fitness distribution of participants.](https://doi.org/10.1371/journal.pone.0227581.g002)

**Fig 2. Fitness distribution of participants.** All participants were classified as sedentary with an average VO$_{2\text{peak}}$ of 34.1 ± 4.0 ml/kg/ min. Our inclusion criteria for 'low fitness' was to achieve a score of "poor" as defined by the Canadian Society for Exercise Physiology (below 41.6 ml/kg/min for males and 35.0 ml/kg/min for females).

**Table 2. Exercise details.**

|                     | HI          | MOD         | Bouts       |
|---------------------|-------------|-------------|-------------|
| Heart rate (bpm)    | "on" 161.5 ± 10.8 | "off" 151.5 ± 12.3 | "on" 130.5 ± 12.0 | "off" 125.5 ± 12.0 | p = 0.001*, g = 2.66 (Wilcoxon) |
| % HR$_{\text{max}}$| 87.1 ± 6.4 | 81.6 ± 6.0 | 70.4 ± 7.0 | 67.7 ± 7.0 | p < 0.001*, g = 2.44 (paired-t-test) |
| RPE (0–10)          | 5.5 ± 1.3 | 3.5 ± 1.9 | 3.5 ± 1.7 | 2.7 ± 1.9 | p < 0.001*, g = 1.13 (paired t-test) |
| Power (W)           | 144.9 ± 28.8 | 50 | 78.5 ± 15.6 | 50 | p < 0.001*, g = 4.26 (Wilcoxon) |
| % of W$_{\text{peak}}$| 68.6 ± 5.5% | 24.3 ± 4.3% | 37.3 ± 4.3% | 24.3 ± 4.3% | p < 0.001*, g = 6.18 (Wilcoxon) |
| EMG$_{\text{exercise}}$| 62.9 ± 7.6 | 62.6 ± 6.0 | p = 0.55, g = 0.05 (Wilcoxon) |

Data are means ± SD. N = 19. g: Hedge's g effect size; HI: High-Intensity interval exercise; MOD: Moderate-Intensity interval exercise; bpm: beats per minute; RPE: Ratings of Perceived Exertion; EMG$_{\text{exercise}}$: EMG of right FDI during exercise intervention; "on": on intervals; "off": off intervals; W$_{\text{peak}}$: peak power

* indicates significance.

https://doi.org/10.1371/journal.pone.0227581.t002
Fig 3. MEP recruitment curves. Data are shown as mean ± standard error. A) HI and MOD did not induce a significant change in AURC. B) Percent change in AURC (i.e. T0 to T1) was not different between HI and MOD. C) Individual data showing variable responses in AURC to HI and MOD.

https://doi.org/10.1371/journal.pone.0227581.g003
Discussion

This is the first study to directly compare the effect of acute HI or MOD on exercise-induced neuroplasticity in low fit, young adults. The results suggest that, regardless of intensity, acute exercise does not alter corticospinal excitability.

Our results show that corticospinal excitability was unaltered by either MOD or HI. This is in line with previous work showing no change in corticospinal excitability following moderate-[3–6] and high-intensity exercise [10] in low fit individuals. Increases in corticospinal excitability following exercise have only been observed in high fit individuals after moderate-intensity exercise [6,8,9], although some studies have reported to change after moderate intensity exercise [7,11]. Opie and Semmler (2019) also recently showed increased MEP amplitude after both high-intensity interval training and low-intensity continuous exercise, although fitness of the participant sample tested was not reported. There are physiological differences between high and low fit groups that may explain these effects. Compared to low fit groups, high fit participants have greater brain volume [40–42], cerebral blood flow [43–45], and muscle adaptations which may reduce fatigue [46]. Further, high fit individuals show greater levels of IGF-1 [47] and are believed to have greater BDNF uptake into the central nervous system [17], thereby promoting neuroplasticity.

Although we observed no change in corticospinal excitability following HI or MOD in low fit, young adults, it is important to note that these protocols are capable of inducing functional changes in this population. For example, in this population, high-intensity exercise has been shown to improve motor skill consolidation [10], while moderate-intensity exercise reduces reaction time [48], improves memory [49], motor skill acquisition [2,50], and improves motor memory [51]. We note that our findings are limited to the effects of a single session of exercise. It is possible that multiple sessions of MOD or HI may provide a stronger stimulus capable of evoking neuroplasticity in the motor cortex that was not observed following a single bout. However, we note that 6-weeks of high-intensity interval training in low fit individuals did not alter MEPs [52]. Further, it is important to note that these data were obtained from healthy, low fit, young adults. Li et al. [22] recently showed that fast treadmill walking increases MEPs from the lesioned hemisphere in those with chronic stroke. This suggests that high-intensity exercise is a feasible method to increase motor output in stroke rehabilitation. This is in line with research showing that exercise can be used to prime the motor system to facilitate motor learning [53]. While the present study did not show an increase in motor output following high- or moderate-intensity interval exercise, this highlights the importance for research to determine exercise protocols that are capable of increasing motor output in this population.

Although we intended to acquire data from 22 participants, only 19 were available to us. However, a recent study from MacDonald et al. [9] observed an increase in MEPs after moderate intensity cycling in a sample of 15 participants who ranged from sedentary to fit. Therefore, it is unlikely that the lack of effect we observed is due to a limited sample size. One factor that may contribute to the variability in AURC is biological sex. We did not recruit an equal ratio of male to female participants to investigate the effect of biological sex on our data. However, a recent study has reported no effect of biological sex on exercise-induced neuroplasticity. Another factor that may introduce variability is genetic variation. Those with the BDNF val66met polymorphism show reduced BDNF secretion [54] that is linked to attenuated exercise-induced neuroplasticity responses following high-intensity interval exercise [11] and motor training [55]. We did not determine the distribution of participants presenting the val66met polymorphism, and this is a limitation of the study.
Conclusions

The present study investigated the effects of exercise intensity on neuroplasticity in young, low fit adults. Corticospinal excitability was assessed before and after HI and MOD. Results revealed that acute exercise did not alter corticospinal excitability, regardless of exercise intensity. Therefore, we conclude that low fit adults do not demonstrate exercise-induced neuroplasticity as measured herein.

Acknowledgments

We thank Faryal Zahir, Diana Harasym, Prabhav Gogna, and Elizabeth M. Jenkins for their contributions to this work.

Author Contributions

Conceptualization: Jenin El-Sayes, Claudia V. Turco, Lauren E. Skelly, Martin J. Gibala, Aimee J. Nelson.

Data curation: Jenin El-Sayes, Claudia V. Turco, Lauren E. Skelly, Mitchell B. Locke.

Formal analysis: Jenin El-Sayes, Claudia V. Turco, Aimee J. Nelson.

Funding acquisition: Aimee J. Nelson.

Investigation: Jenin El-Sayes.

Methodology: Jenin El-Sayes, Claudia V. Turco, Aimee J. Nelson.

Supervision: Aimee J. Nelson.

Writing – original draft: Jenin El-Sayes.

Writing – review & editing: Jenin El-Sayes, Claudia V. Turco, Lauren E. Skelly, Mitchell B. Locke, Martin J. Gibala, Aimee J. Nelson.

References

1. Ziemann U, Reis J, Schwenkreis P, Rosanova M, Strafella A, Badawy R, et al. TMS and drugs revisited. 2014. Clinical Neurophysiology. 2015. pp. 1847–1868. https://doi.org/10.1016/j.clinph.2014.08.028 PMID: 25534482

2. Statton MA, Encarnacion M, Celnik P, Bastian AJ. A single bout of moderate aerobic exercise improves motor skill acquisition. PLoS One. 2015; 10: e0141393. https://doi.org/10.1371/journal.pone.0141393 PMID: 26506413

3. McDonnell MN, Buckley JD, Opie GM, Ridding MC, Semmler JG. A single bout of aerobic exercise promotes motor cortical neuroplasticity. J Appl Physiol. 2013; 114: 1174–1182. https://doi.org/10.1152/japplphysiol.01378.2012 PMID: 23493367

4. Singh AM, Duncan RE, Neva JL, Staines WR. Aerobic exercise modulates intracortical inhibition and facilitation in a nonexercised upper limb muscle. BMC Sports Sci Med Rehabil. 2014; 6: 23. https://doi.org/10.1186/2052-1847-6-23 PMID: 25031838

5. Smith AE, Goldsworthy MR, Garside T, Wood FM, Ridding MC. The influence of a single bout of aerobic exercise on short-interval intracortical excitability. Exp Brain Res. 2014; 232: 1875–1882. https://doi.org/10.1007/s00221-014-3879-7 PMID: 24570388

6. Lulic T, El-Sayes J, Fassett HJ, Nelson AJ. Physical activity levels determine exercise-induced changes in brain excitability. PLoS One. 2017; 12: e0173672. https://doi.org/10.1371/journal.pone.0173672 PMID: 28278300

7. Neva JL, Brown KE, Mang CS, Francisco BA, Boyd LA. An acute bout of exercise modulates both intracortical and interhemispheric excitability. Eur J Neurosci. 2017; 45: 1343–1355. https://doi.org/10.1111/ejn.13568 PMID: 28370864
18. Ferris LT, Williams JS, Shen CL. The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. Med Sci Sports Exerc. 2007; 39: 728–734. https://doi.org/10.1249/mss.0b013e31802f04c7 PMID: 17414812

19. Skriver K, Roig M, Lundbye-Jensen J, Pingel J, Helge JW, Kiens B, et al. Acute exercise improves motor memory: Exploring potential biomarkers. Neurobiol Learn Mem. 2014; 116: 46–58. https://doi.org/10.1016/j.nlm.2014.08.004 PMID: 25128877

20. Thomas R, Johnsen LK, Geertsen SS, Christiansen L, Ritz C, Roig M, et al. Acute exercise and memory consolidation: The role of exercise intensity. PLoS One. 2016; 11: e0159589. https://doi.org/10.1371/journal.pone.0159589 PMID: 27454423

21. Do Lee C, Folsom AR, Blair SN. Physical activity and stroke risk: A meta-analysis. Stroke. 2003; 34: 2475–2481. https://doi.org/10.1161/105932102.012051 PMID: 12844959

22. Li X, Charalambous CC, Reisman DS, Morton SM. A short bout of high-intensity exercise alters ipsilesional motor cortical excitability post-stroke. Top Stroke Rehabil. 2019; https://doi.org/10.1080/10790104.2019.1623456 PMID: 31144609

23. Macniss MJ, Gibala MJ. Physiological adaptations to interval training and the role of exercise intensity. J Physiol. 2017; 595: 2915–2930. https://doi.org/10.1113/jphysiol.2016.132099 PMID: 2774956

24. Saucedo Marquez CM, Vanaudenaerde B, Troosters T, Wenderoth N. High-intensity interval training evokes larger serum BDNF levels compared with intense continuous exercise. J Appl Physiol. 2015; 119: 1363–1373. https://doi.org/10.1152/japplphysiol.00116.2014 PMID: 26472862

25. Combes A, Dekkerle J, Webborn N, Watt P, Bougault V, Daussin FN. Exercise-induced metabolic fluctuations influence AMPK, p38-MAPK and CaMKII phosphorylation in human skeletal muscle. Physiol Rep. 2015; 3. https://doi.org/10.14814/phy2.12462 PMID: 26359238

26. Jimenez-Pavon D, Lovie CJ. High-intensity intermittent training versus moderate-intensity intermittent training: Is it a matter of intensity or intermittent efforts? Br J Sports Med. 2017; 51: 1319–1320. https://doi.org/10.1136/bjsports-2016-097015 PMID: 28137785

27. Boyne P, Meyrose C, Westover J, Whitesel D, Hatter K, Reisman DS, et al. Exercise intensity affects acute neurotrophic and neurophysiological responses poststroke. J Appl Physiol. 2018; 126: 431–443. https://doi.org/10.1152/japplphysiol.00594.2018 PMID: 30571289
Exercise intensity does not impact neuroplasticity in low fit adults

28. Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia. 1971; 9: 97–113. https://doi.org/10.1016/0028-3932(71)90064-7 PMID: 5146491

29. CSEP. CSEP-PARTH Physical Activity Training for Health. 2013.

30. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Group TS of TMSC. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clinial Neurophysiol. 2009; 120: 2008–2039.

31. Warburton DER, Gledhill N, Jamnik VK, Bredin SSD, McKenzie DC, Stone J, et al. Evidence-based risk assessment and recommendations for physical activity clearance: Consensus Document 2011. Appl Physiol Nutr Metab. 2011; 36: S266–S298. https://doi.org/10.1139/h11-062 PMID: 21800945

32. Gillen JB, Percival ME, Skelly LE, Martin BJ, Tan RB, Tarnopolsky MA, et al. Three minutes of all-out intermittent exercise per week increases skeletal muscle oxidative capacity and improves cardiometabolic health. PLoS One. 2014; 9: e111489. https://doi.org/10.1371/journal.pone.0111489 PMID: 25365337

33. Allison MK, Baglole JH, Martin BJ, MacInnis MJ, Gurd BJ, Gibala MJ. Brief Intense Stair Climbing Improves Cardiorespiratory Fitness. Med Sci Sports Exerc. 2017; 49: 298–307. https://doi.org/10.1249/MSS.000000000001188 PMID: 28009784

34. Craig Marshall A. L., Sjöström M., Bauman A. E., Booth M. L., Ainsworth B. E., et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003; 35: 1381–1395. Available: http://ovidsp.ovid.com.proxy1.cl.msu.edu/spb/ovidweb.cgi?WebLinkFrameset=1&S=PLMPFPGFELDHDHEINCLFLMBJUBPHEA00&returnUrl=http%3A%2F%2Fovidsp.tx.ovid.com%2Fspdb%2Fovidweb.cgi%3F%26TOC%3Dsh.15.16.21.4%252C%2520%252C%2520%26FORMAT%3Dtoc%26FIELDS%3D%26FIELD%3D%253DP https://doi.org/10.1249/01.MSS.0000078924.61453.FB PMID: 12900694

35. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. Quantity and quality of exercise for developing and maintaining cardiorehabilitative, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. Med Sci Sports Exerc. 2011; 43: 1334–1359. https://doi.org/10.1249/MSS.0b013e3182e2939a PMID: 21894556

36. Mang CS, McEwen LM, Maclsaa JL, Snow NJ, Campbell KL, Kobor MS, et al. Exploring genetic influences underlying acute aerobic exercise effects on motor learning. Sci Rep. 2017; 7: 12123. https://doi.org/10.1038/s41598-017-12422-3 PMID: 28935933

37. Borg G. Psychophysical scaling with applications in physical work and the perception of exertion. Scandinavian Journal of Work, Environment and Health. 1990. pp. 55–58. https://doi.org/10.5271/sjweh.1815 PMID: 2245867

38. Turco CV, El-Sayes J, Locke MB, Chen R, Baker S, Nelson AJ. Effects of lorazepam and baclofen on short- and long-latency afferent inhibition. J Physiol. 2018; 596. https://doi.org/10.1113/JP276710 PMID: 30192398

39. Abdoli-Eramaki M, Damecour C, Christenson J, Stevenson J. The effect of perspiration on the sEMG amplitude and power spectrum. J Electromyogr Kinesiol. 2012; 22: 908–913. https://doi.org/10.1016/j.jelekin.2012.04.009 PMID: 22613823

40. Colcombe SJ, Erickson KI, Scaf FE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. Journals Gerontol—Ser A Biol Sci Med Sci. 2006; 61: 1166–1170. https://doi.org/10.1093/gerona/61.11.1166 PMID: 17167157

41. Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter volume. Neurobiol Aging. 2014; 35: S20–28. https://doi.org/10.1016/j.neurobiolaging.2014.03.034 PMID: 24952993

42. Sexton CE, Betts JF, Demnitz N, Dawes H, Ebmeier KP, Johansen-Berg H. A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the aging brain. Neuroimage. 2016; 131: 81–90. https://doi.org/10.1016/j.neuroimage.2015.09.071 PMID: 26477656

43. Chapman SB, Aslan S, Spence JS, DeFina LF, Keeler MW, Didehbani N, et al. Shorter term aerobic exercise improves brain, cognition, and cardiovascular fitness in aging. Front Aging Neurosci. 2013; 5; 75. https://doi.org/10.3389/fnagi.2013.00075 PMID: 24282403

44. Thomas BP, Yozhuvath US, Tseng BY, Liu P, Levine BD, Zhang R, et al. Life-long aerobic exercise preserved baseline cerebral blood flow but reduced vascular reactivity to CO2. J Magn Reson Imaging. 2013; 36: 1177–1183. https://doi.org/10.1002/jmri.24090 PMID: 23528611

45. Zimmerman B, Sutton BP, Low KA, Fletcher MA, Tan CH, Schneider-Garces N, et al. Cardiorespiratory fitness mediates the effects of aging on cerebral blood flow. Front Aging Neurosci. 2014; 6; 59. https://doi.org/10.3389/fgene.2014.00059 PMID: 24776817

46. Petriz BA, Gomes CPC, Almeida JA, de Oliveira GP, Ribeiro FM, Pereira RW, et al. The Effects of Acute and Chronic Exercise on Skeletal Muscle Proteome. J Cell Physiol. 2017; 232: 257–269. https://doi.org/10.1002/jcp.25477 PMID: 27381298
47. Ardawi MSM, Rouzi AA, Qari MH. Physical activity in relation to serum sclerostin, insulin-like growth factor-1, and bone turnover markers in healthy premenopausal women: A cross-sectional and a longitudinal study. J Clin Endocrinol Metab. 2012; 97: 3691–3699. https://doi.org/10.1210/jc.2011-3361 PMID: 22865898

48. Ozymisci-Taskiran O, Gunendi Z, Bolukbasi N, Beyazova M. The effect of a single session submaximal aerobic exercise on premotor fraction of reaction time: An electromyographic study. Clin Biomech. 2008; 23: 231–235. https://doi.org/10.1016/j.clinbiomech.2007.08.027 PMID: 17961893

49. Nanda B, Balde J, Manjunatha S. The acute effects of a single bout of moderate-intensity aerobic exercise on cognitive functions in healthy adult males. J Clin Diagnostic Res. 2013; 7: 1883–1885. https://doi.org/10.7860/JCDR/2013/5855.3341 PMID: 24179888

50. Snow NJ, Mang CS, Roig M, McDonnell MN, Campbell KL, Boyd LA. The effect of an acute bout of moderate-intensity aerobic exercise on motor learning of a continuous tracking task. PLoS One. 2016; 11: e0150039. https://doi.org/10.1371/journal.pone.0150039 PMID: 26901664

51. Mang CS, Snow NJ, Wadden KP, Campbell KL, Boyd LA. High-Intensity Aerobic Exercise Enhances Motor Memory Retrieval. Med Sci Sports Exerc. 2016; 48: 2477–2486. https://doi.org/10.1249/MSS.0000000000000104 PMID: 27414689

52. Nicolini C, Toepp S, Harasym D, Michalski B, Fahnestock M, Gibala M, et al. No changes in corticospinal excitability, biochemical markers and working memory after six weeks of high-intensity interval training in sedentary males. Physiol Rep. 2019; 7: e14140. https://doi.org/10.14814/phy2.14140 PMID: 31175708

53. Stoykov ME, Madhavan S. Motor priming in neurorehabilitation. J Neurol Phys Ther. 2015; 39: 33–42. https://doi.org/10.1097/NPT.0000000000000065 PMID: 25415511

54. Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 2003; 112: 257–269. https://doi.org/10.1016/s0092-8674(03)00035-7 PMID: 12553913

55. Kleim JA, Chan S, Pringle E, Schallert K, Procaccio V, Jimenez R, et al. BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex. Nat Neurosci. 2006; 9: 735–737. https://doi.org/10.1038/nn1699 PMID: 16680163