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Neurophysiological effects of acute aerobic exercise in young adults: a systematic review and meta-analysis

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ABSTRACT

Evidence continues to accumulate that acute aerobic exercise (AAE) impacts neurophysiological excitability as measured by transcranial magnetic stimulation (TMS). Yet, uncertainty exists about which TMS measures are modulated after AAE in young adults. The influence of AAE intensity and duration of effects are also uncertain. This pre-registered meta-analysis (CRD42017065673) addressed these uncertainties by synthesizing data from 23 studies (including 474 participants) published until February 2024. Meta-analysis was run using a random-effects model and Hedge's g used as effect size. Our results demonstrated a decrease in short-interval intracortical inhibition (SICI) following AAE ($g = 0.27$; 95 % CI [0.16–0.38]; $p < .0001$), particularly for moderate ($g = 0.18$; 95 % CI [0.05–0.31]; $p < .01$) and high ($g = 0.49$; 95 % CI [0.27–0.71]; $p < .0001$) AAE intensities. These effects remained for 30 minutes after AAE. Additionally, increased corticospinal excitability was only observed for high intensity AAE ($g = 0.28$; 95 % CI, [0.07–0.48]; $p < .01$). Our results suggest potential mechanisms for inducing a more susceptible neuroplastic environment following AAE.

1. Introduction

Acute aerobic exercise (AAE) can improve cognitive performance (Kamijo et al., 2009; Kamijo et al., 2004; Kamijo et al., 2007; Yanagisawa et al., 2010), motor performance (Mang et al., 2014; Statton et al., 2015), and motor learning (Mang et al., 2014; Neva et al., 2019; Skriver et al., 2014; Stavrinos and Coxon, 2017; Thomas et al., 2016; Wanner et al., 2020). More specifically, several studies showed that AAE performed close in time to task practice improves motor learning (Roig et al., 2012; Thomas et al., 2016). Many studies have further investigated the changes that occur in brain function (i.e., neuroplasticity) following AAE to understand the underlying neural mechanisms of this beneficial effect to motor learning (Chen et al., 2019; Wrann et al., 2013). Previous work investigated neuroplasticity that occurs following AAE using several measurement techniques (Basso and Suzuki, 2017), including electroencephalography (Crabbe and Dishman, 2004), functional magnetic resonance imaging (Voss et al., 2020) and various forms of transcranial magnetic stimulation (TMS; (Andrews et al., 2020; Mang et al., 2014; Singh et al., 2014)). Notably, the number of studies evaluating TMS-based neurophysiological excitability changes following AAE has been rapidly increasing in the past decade, demonstrating a growing interest in this field (Andrews et al., 2020; El-Sayes et al., 2019; Kuo et al., 2023; Mang et al., 2014; McDonnell et al., 2013; Mooney et al., 2016; Morris et al., 2020; Neva et al., 2017; Neva et al., 2021;

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Nicolini et al., 2020; Singh et al., 2014; Smith et al., 2014; Yamazaki et al., 2019).

Transcranial magnetic stimulation has been an important tool for understanding the effects of AAE on the human brain. TMS is a non-invasive technique that can both quantify and modulate cortical excitability (Brown et al., 2014; Di Lazzaro and Ziemann, 2013; Ridding and Rothwell, 1997). Following AAE, the response to plasticity-inducing repetitive TMS protocols can be increased (Andrews et al., 2020; Hendrikse et al., 2017; Mang et al., 2014; McDonnell et al., 2013; Singh et al., 2014), which suggests that AAE may prepare or 'prime' the brain for enhanced plasticity changes and motor learning. Studies have attempted to further elucidate the underlying neurophysiological mechanisms of this enhanced neuroplasticity following AAE by assessing changes in various measures of primary motor cortex (M1) excitability (Andrews et al., 2020; Lulic et al., 2017; Mooney et al., 2016; Morris et al., 2020; Singh et al., 2014; Smith et al., 2014). Importantly, each of the different TMS measures of M1 excitability (see Table 1 and Fig. 2) reflect unique underlying neurophysiological mechanisms (Brown et al., 2014; Di Lazzaro and Ziemann, 2013; Neva et al., 2020; Ridding and Rothwell, 1997). These changes in intra- and inter-hemispheric M1 excitability, via single and paired-pulse TMS measures, have been interpreted as early markers of rapid neuroplasticity following AAE (Andrews et al., 2020; Kuo et al., 2023; McDonnell et al., 2013; Mooney et al., 2016; Neva et al., 2017; Nicolini et al., 2020; Singh et al., 2014; Smith et al., 2014; Yamazaki et al., 2019).

Several neural mechanisms may underpin the impact of AAE on neuroplasticity in young adults as measured by TMS. For example, AAE can decrease measures of M1 inhibition via assessment of short-interval intracortical inhibition [SICI; (El-Sayes et al., 2019; Hendy et al., 2022; Kuo et al., 2023; Lulic et al., 2017; Singh et al., 2014; Smith et al., 2014; Stavrinos and Coxon, 2017; Yamazaki et al., 2019)], long-interval intracortical inhibition [LICI; (Mooney et al., 2016)] and the contralateral silent period (Neva et al., 2017). AAE can increase measures of M1 facilitation as shown by assessment of intracortical facilitation [ICF; (Andrews et al., 2020; Kuo et al., 2023; Morris et al., 2020; Singh et al., 2014)] and short-interval intracortical facilitation [(SICF; (Neva et al., 2017)]. Other work showed that the effects of AAE extend to inter-hemispheric inhibition, as the ipsilateral silent period decreases bilaterally following AAE (Neva et al., 2017). Further, paired-pulse and dual-site TMS studies showed that inhibitory connectivity to M1 from other regions such as the somatosensory cortex (Brown et al., 2020; Yamazaki et al., 2019) and the cerebellum (Mang et al., 2016) are modulated following AAE. However, it is important to highlight that the effects of AAE on measures of M1 excitability are not consistent across all studies. In contrast to the majority of studies, Mooney et al., (2016), Morris et al. (2020), and Neva et al. (2021) reported no decrease in SICI (Mooney et al., 2016; Morris et al., 2020; Neva et al., 2021). Further, it is currently unclear whether measures of corticospinal excitability (e.g., peak-to-peak motor evoked potential [MEP] amplitude) are altered following AAE (Andrews et al., 2020; Kuo et al., 2023; Mang et al., 2014; Nicolini et al., 2020; Ostadan et al., 2016; Singh et al., 2016; Smith et al., 2018). Consequently, there remains uncertainty regarding which TMS measures are impacted by AAE across studies in young adults, and hence are most consistently modulated.

Studies have tested various intensities and types of AAE, which may influence the observed effects on TMS-based measures of M1 excitability. Specifically, studies have implemented a range of AAE intensities, including low (MacDonald et al., 2019; McDonnell et al., 2013; Morris et al., 2020; Yamazaki et al., 2019), moderate (Andrews et al., 2020; Brown et al., 2020; El-Sayes et al., 2020, 2019; Kuo et al., 2023; Lulic et al., 2017; MacDonald et al., 2019; McDonnell et al., 2013; Mooney et al., 2016; Neva et al., 2017; Neva et al., 2021; Singh et al., 2016; Singh et al., 2014; Smith et al., 2014), and high (Andrews et al., 2020; El-Sayes et al., 2020; Hendy et al., 2022; Mang et al., 2016, 2014; Nicolini et al., 2020; Ostadan et al., 2016; Smith et al., 2014, 2018; Stavrinos and Coxon, 2017). Moreover, studies have implemented

Table 1
Single and paired-pulse transcranial magnetic stimulation techniques presented along with their associated neurophysiological mechanisms and protocols.

TMS measure	Neurophysiological measure	Underlying mechanism	Protocol for TMS measure
Single-pulse			
Resting motor threshold (RMT)[1]	Corticospinal excitability	Direct and transsynaptic activation of pyramidal neurons of central core of M1 representation[1]	Minimal %MSO required to achieve five out of ten consecutive MEPs ≤50 μV (peak-to-peak)
Active motor threshold (AMT)[1]	Corticospinal excitability	Direct and transsynaptic activation of pyramidal neuron of central core of M1 representation[1]	Minimal %MSO required to achieve five out of ten consecutive MEPs ≤200 μV (peak-to-peak) while holding a light contraction
Cortical silent period (CSP)[2]	Silent period in ongoing muscle activation	Spinal mechanisms (first half) and cortical mechanisms (latter half) mediated by $GABA_B$ receptors[3]	Suprathreshold single pulse delivered over M1 (between ~120–150 % RMT/AMT) collected during a light contraction (10–20 % MVC) of the contralateral target muscle
Ipsilateral silent period (iSP)[4]	Silent period in ongoing muscle activation; transcallosal inhibition	$GABA_B$ receptor-mediated activity and unknown mechanisms[5]	Suprathreshold single pulse delivered over M1 (~130–150 % RMT) that is ipsilateral to the target muscle (relative to the stimulated hemisphere) that is performing a moderate contraction (~50 % MVC)
Paired-pulse			
Short-interval intracortical inhibition (SICI)[6]	Intracortical inhibition	$GABA_A$ receptor-mediated activity[7]	CS at subthreshold intensity (e.g., 80 % RMT) followed by a TS at suprathreshold intensity (% MSO to elicit 1 mV MEP), with an ISI ranging from 1 to 6 ms
Long-interval intracortical inhibition (LICI)[8]	Intracortical inhibition	$GABA_B$ receptor-mediated activity[9]	CS and TS at suprathreshold intensity (% MSO to elicit 1 mV MEP) with an ISI ranging from 50 and 200 ms
Intracortical facilitation (ICF)[10]	Intracortical facilitation	Glutamate, I-wave propagation,	CS at subthreshold intensity (e.g.,

(*continued on next page*)

Table 1 (*continued*)

TMS measure	Neurophysiological measure	Underlying mechanism	Protocol for TMS measure
		serotonin, other mechanisms[11]	80 % RMT) followed by TS at suprathreshold intensity (% MSO to elicit 1 mV MEP) with an ISI ranging from 10 to 15 ms
Short-interval intracortical facilitation (SICF)[12]	Intracortical facilitation	$GABA_A$ receptor-mediated activity, I-wave propagation[13]	CS at suprathreshold intensity (% MSO to elicit 1 mV MEP) followed by TS at threshold or subthreshold (e.g., 90 % RMT) intensity with ISI at discrete intervals (e.g., 1.1–1.5, 2.3–3.0, and 4.1–4.5 ms)
Interhemispheric inhibition (IHI)[4]	Interhemispheric inhibition	Short latency IHI (~10 ms ISI): unknown Long latency IHI (20–50 ms ISI): $GABA_B$-mediated[14]	CS at suprathreshold intensity at M1 in one hemisphere followed by a TS at suprathreshold intensity at the opposite M1. Suprathreshold intensities can be delivered at a %MSO to elicit 1 mV MEP
Cerebellar inhibition (CBI)[15]	Inhibition of motor cortex by the cerebellum	Purkinje fiber activation, cerebellar-thalamic-cortical pathway[16][17]	CS is delivered at slightly below the maximum tolerated intensity, followed by a TS at an intensity that evokes a 1 mV MEP, with ISI ranging from 5 to 8 ms.
Short afferent inhibition (SAI)[18]	Sensorimotor integration	$GABA_A$ receptor-mediated activity, acetylcholine[19]	Peripheral nerve stimulation is followed by single pulse stimulation with ISI ranging from 18 to 25 ms
Long afferent inhibition (LAI)[20]	Sensorimotor integration	$GABA_A$ receptor-mediated activity[19]	Peripheral nerve stimulation is followed by single pulse stimulation with ISI ranging from 200 to 1000 ms

Abbreviations: TMS = Transcranial magnetic stimulation; MSO = maximal stimulator output; RMT = resting motor threshold; AMT = active motor threshold; MVC = maximum voluntary contraction. MEPs = motor evoked potentials; ISI = interstimulus interval; CS = conditioning stimulus; TS = test stimulus; M1 = primary motor cortex; GABA = gamma-aminobutyric acid.
References: [1]: (Rossini et al., 1994); [2]: (Cantello et al., 1992); [3]: (Ziemann et al., 1996b); [4]: (Ferbert et al., 1992); [5]: (Meyer et al., 1995); [6]: (Kujirai et al., 1993); [7]: (Ziemann et al., 1996a); [8]: (Wassermann et al., 1996); [9]: (Roick et al., 1993); [10]: (Nakamura et al., 1997); [11]: (Ziemann et al., 1998); [12]: (Hanajima et al., 2002); [13]: (Ilić et al., 2002); [14]: (De Gennaro et al., 2004); [15]: (Amassian et al., 1992); [16]: (Ugawa et al., 1991); [17]: (Spampinato et al., 2020); [18]: (Delwaide and Olivier, 1990); [19]: (Turco et al., 2018); [20]: (Chen et al., 1999)

different exercise types, including continuous and interval (i.e., alternating bouts of active work and active/passive recovery) AAE (see Table 2). While several studies found a decrease in SICI (see Table 2), others have found no modulation when high- (Nicolini et al., 2020) or moderate- (Neva et al., 2021) -intensity AAE was performed. Further, LICI modulation was found following moderate-intensity AAE (Mooney et al., 2016), while others found no modulation when moderate- (Singh et al., 2014) or high-intensity (Stavrinos and Coxon, 2017) AAE was performed. Some studies found increased ICF following moderate- (Morris et al., 2020; Singh et al., 2014) and high-intensity (Andrews et al., 2020) AAE, while others found no modulation of ICF after high-intensity AAE or decreased ICF after moderate-intensity (Lulic et al., 2017) AAE. Finally, whether AAE at any intensity or type impacts corticospinal excitability via motor-evoked potential (MEP) amplitude change is unclear. Some studies show enhanced corticospinal excitability following AAE (El-Sayes et al., 2019; Hendy et al., 2022; Lulic et al., 2017; MacDonald et al., 2019; Nicolini et al., 2020; Ostadan et al., 2016), while most studies show no change (Andrews et al., 2020; Brown et al., 2020; El-Sayes et al., 2020; Kuo et al., 2023; Mang et al., 2014; McDonnell et al., 2013; Morris et al., 2020; Neva et al., 2017, 2021; Singh et al., 2016, 2014; Smith et al., 2014, 2018; Stavrinos and Coxon, 2017; Yamazaki et al., 2019). Therefore, a synthesis of the available data is necessary to understand the influence of intensity and type of AAE on TMS-based measures of M1 excitability. Since the vast majority of the studies evaluating the effect of AAE on these cortical excitability measures included healthy young adults, we aimed to investigate the neurophysiological effects that occur following a single bout of exercise in a healthy population.

Although many reviews concerning aerobic exercise and its effects on M1 excitability measured with TMS are already present in the field (Alibazi et al., 2021; Mellow et al., 2020; Nicolini et al., 2021; Turco and Nelson, 2021), no meta-analysis has been performed on the effects of aerobic exercise alone on M1 excitability. Thus, the overall objective of the present systematic review and meta-analysis was to identify the impact of AAE alone on TMS-based measures of M1 excitability based on a synthesis of the current state of literature. Specifically, this meta-analysis had three aims, which were to: (1) determine which TMS measure(s) show(s) the most consistent effects following AAE, (2) examine which AAE intensity (i.e., low, moderate, high) elicits the greatest response in M1 excitability, and (3) explore the duration of the M1 excitability effect following AAE.

2. Methods

The present systematic review and meta-analysis was pre-registered in the international prospective register of systematic reviews (PROSPERO) under the registration number CRD42017065673 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=65673). This study was reported following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021).

2.1. Search strategy

A comprehensive systematic literature search was performed by DA across four electronic databases: Medline (Ovid), Embase (Ovid), CINAHL Complete (Ebsco) and APA PsycInfo (PsycNet) on May 7, 2020, and subsequently updated on February 24, 2023 and January 22, 2024. Articles considered for inclusion needed to be in either English or French, published in peer-reviewed journals, with no restrictions on the publication year. For the literature search, the first category of keywords was acute aerobic exercise, specifically lower limb cycling exercise, and

Table 2
Characteristics of the studies included in the meta-analysis.

Study	Participants		Exercise intervention			TMS		
Author, year	Sample Size (n)	Age (mean ± SD years)	Duration (min)	Intensity	Control	Time of measure	Measured variables	Outcome
Andrews et al., (2020)	20 (M: 9, F: 11)	35 ± 13	20	High *(interval training: 3 min at 50 % age-predicted HRR and 2 min up to age-predicted 90 % HRR)* Moderate *(20 min; 50 % age-predicted HRR)*	Rest	Post 1	- MEP - $SICI_{2\ ms}$ - LICI - ICF	- - - ↗ for High
Brown et al., (2020)	24 (M: 10, F: 14)	26 ± 5	20	Moderate *(65–70 % age-predicted MHR)*	Rest	Post 1	- MEP - SAI - LAI - AF	- - ↗ -
El-Sayes et al., (2019)	34 (M: 17, F: 17)	21 ± 2	20	Moderate *(65–70 % age-predicted MHR)*	NA	Post 1	- MEP - $SICI_{2\ ms}$	↗ ↘
El-Sayes et al., (2020)	19 (M: 12, F: 7)	22 ± 3	20	High *(interval training: 1 min at 80–100 % age-predicted MHR and 1 min at 50 W)* Moderate *(interval training: 1 min at 60–79 % age-predicted MHR and 1 min at 50 W)*	NA	Post 1	- RMT - MEP	- -
Hendy et al., (2022)	19 (M: 9, F: 10)	23 ± 3	20	High *(interval training: 2 min at 80 % of age-predicted MHR and 2 min of active recovery with no resistance)*	Rest	Post 1	- MEP - $SICI_{3\ ms}$	↗ ↘
Kuo et al., (2023)	20 (M: 10, F: 10)	26 ± 1	20	Moderate *(61–74 % age-predicted MHR)*	Rest	Post 1	- RMT - AMT - MEP - $SICI_{2\ ms}$ -$SICI_{3\ ms}$ -$SICI_{5\ ms}$ -$ICF_{10\ ms}$ - $ICF_{15\ ms}$	- - - ↘ ↘ - ↗ ↗
Lulic et al., (2017)	High PAL: 14 (M: 5, F: 9) Low PAL: 14 (M: 6, F: 8)	22 ± 3 21 ± 1	20	Moderate *(50–70 % age-predicted MHR)*	NA	Post 1	- RMT - AMT - MEP - $SICI_{2\ ms}$ - $SICF_{1.2\ ms}$ - $SICF_{2.5\ ms}$ - ICF	↗ for High PAL - ↗ for High PAL ↘ for both - - ↘
MacDonald et al., (2019)	29 (M: 15, F: 14)	26 ± 3	20	Low *(30 % age-predicted HRR)* Moderate *(40 % and 50 % age-predicted HRR)*	NA	Post 1	- MEP	↗ for Mod
Mang et al., (2014)	16 (M: 8, F: 8)	24 ± 4	20	High *(interval training; 3 min at 90 % max PO and 2 min at 50 W)*	Rest	Post 1	- MEP	-
Mang et al., (2016)	34 (M: 14, F: 20)	25 ± 4	20	High *(interval training; 3 min at 90 % max PO and 2 min at 50 W)*	Rest	Post 1	- CBI	↘
McDonnell et al., (2013)	25 (M: 9, F: 16)	27 ± 8	30 15	Low *(57 % age-predicted MHR)* Moderate *(77 % age-predicted MHR)*	Rest	Post 1	- MEP	-
Mooney et al., (2016)	10 (M: 7, F: 3)	23 ± 2	30	Moderate *(60 % of measured VO_2 peak)*	Rest	Post 1 Post 2	- $SICI_{1\ ms}$ - $SICI_{2.5\ ms}$ - LICI - cSP	- - ↘ -
Morris et al., (2020)	14 (M: 5, F: 9)	26 ± 3	30	Moderate *(40–60 % age-predicted HRR)*	Rest	Post 3	- RMT - MEP - $SICI_{3\ ms}$ - LICI - ICF	- - - - ↗
Neva et al., (2017)	12 (M: 6, F: 6)	26 ± 4	20	Moderate *(65–70 % age-predicted MHR)*	NA	Post 1	- MEP - SICF - cSP - iSP	- ↗ at ISI 1.5 ms ↘ ↘
Neva et al., (2021)	24 (M: 12, F: 12)	27 ± 6	25	Moderate *(65–70 % age-predicted MHR)*	Rest	Post 1	- MEP -$SICI_{2\ ms}$	- -

(*continued on next page*)

Table 2 (*continued*)

Study	Participants		Exercise intervention			TMS		
Author, year	Sample Size (n)	Age (mean ± SD years)	Duration (min)	Intensity	Control	Time of measure	Measured variables	Outcome
Nicolini et al., (2020)	21 (M: 21, F: 0)	23 ± 3	17.5	High *(interval training: 1 min at 105–125 % W_{peak} and 1.5 min at 30 % W_{peak})*	Rest	Post 1	-RMT -AMT -MEP -$SICI_{2\ ms}$ -ICF	- - ↗ - -
Ostadan et al., (2016)	18	23 ± 4	15	High *(interval training: 3 min at 85–90 % VO_{2peak} and 2 min at 25 % maximum workload)*	Rest	Post 1 Post 2 Post 3	- MEP	↗
Singh et al., (2014)	12 (M: 7, F: 5)	28	20	Moderate *(65–70 % age-predicted MHR)*	NA	Post 1	- MEP -$SICI_{2.5\ ms}$ - LICI - ICF	- ↘ - ↗
Singh et al., (2016)	25 (M: 14, F: 11)	27	20	Moderate *(65–70 % age-predicted MHR)*	Training task	Post 2	- MEP	-
Smith et al., (2014)	13 (M: 7, F: 6)	25 ± 5	30	Moderate *(40 % of predicted HRR)* High *(80 % of predicted HRR)*	NA	Post 1	- RMT - MEP - $SICI_{2\ ms}$ - $SICI_{3\ ms}$	- - ↘ for Mod ↘
Smith et al., (2018)	18 (M: 9, F: 9)	25 ± 5	30	High *(80 % predicted HRR)*	Rest	Post 1	- MEP	-
Stavrinos and Coxon, (2017)	24 (M: 14, F: 10)	24 ± 4	20	High *(interval training: 2 min at 90 % age-predicted HRR and 3 min at 50 % age-predicted HRR)*	Rest	Post 1	- MEP - $SICI_{1\ ms}$ - $SICI_{2\ ms}$ - LICI	- - ↘ -
Yamazaki et al., (2019)	15 (M: 7, F: 8)	22 ± 2	30	Low *(30 % of measured VO_{2peak})*	Rest	Post 1 Post 2	- RMT - MEP - $SICI_{2\ ms}$ - LICI - ICF - SICF - SAI	- - ↘ - ↘ - ↘
	Total: 474 *Reported* (M: 233, W: 223)	Average 25 ± 4	Average 22 ± 5					

TMS = transcranial magnetic stimulation; M = Male, F = Female; HRR = heart rate reserve; MHR=maximal heart rate; W = watts. Exercise type is continuous unless otherwise stated. The outcome is obtained following exercise intervention. M= males; F=females. Rest refers to seated rest. NA = not available. Post 1= 0–30 min post-exercise; Post 2= 31–60 min post-exercise; Post 3= > 61 min post-exercise; RMT = resting motor threshold; AMT = active motor threshold; MEP = motor evoked potentials; SICI = short-interval intracortical inhibition; LICI = long-interval intracortical inhibition; ICF = intracortical facilitation; SICF = short-interval intracortical facilitation; SAI = short afferent inhibition; cSP = cortical silent period; iSP = ipsilateral silent period; 1 ms, 2 ms, 2.5 ms, 3 ms, 5 ms refer to the different inter-stimulus intervals. Mod = moderate. ↗ = significant increase following exercise; ↘ = significant decrease following exercise; - = no significant change following exercise.

included the following terms: *acute aerobic exercise, acute physical exercise, acute exercise bouts*. The second category of keywords was related to the neurophysiological measurements and included the following terms: *transcranial magnetic stimulation, cortex excitability, intracortical excitability, motor-evoked potentials, intracortical facilitation, intracortical inhibition, interhemispheric excitability, interhemispheric inhibition.* The combination of keywords, Medical Subject Headings (Mesh) terms and the search equations are available in the Supplementary Material.

2.2. Selection criteria

Two reviewers (LY & NH) independently screened all studies identified using the online platform Covidence (Veritas Health, 2023). Articles were included if both reviewers agreed on their eligibility which was conducted by first screening the title and abstract, followed by the full text screening. If there was a disagreement, a third reviewer (JN) intervened to reach an agreement. The overall systematic review process was reported in the PRISMA flowchart (Fig. 1).

2.3. Eligibility criteria

This systematic review and meta-analysis included studies that met the following PICOS inclusion criteria Fig. 2.

2.3.1. Participants

Young healthy individuals (18–40 years old) without any neurological or musculoskeletal disorders were included. Some studies included participants above 40 years. However, this was rare and usually included only a few participants within a single study. Moreover, we decided to include these studies in our meta-analysis since the average age of all studies were within our specified range.

2.3.2. Intervention

The intervention consisted of a single session of lower limb cycling exercise at any exercise intensity and any type. Lower-limb cycling exercise and TMS-based measurements taken from the non-exercised upper-limb was chosen as the focus of this meta-analysis for two main reasons. Firstly, since the leg muscles are the largest muscles in our body, it is known that performing exercise involving the legs (e.g., leg cycling) is likely to induce a robust aerobic response (Andersen and Saltin, 1985; Grimby et al., 1966). Secondly, it has been shown that simple muscle contractions (either isometric or dynamic) and/or repeated movements (i.e., ballistic thumb abduction task) can induce changes in cortical excitability (Iezzi et al., 2008; Koeneke et al., 2006; Rogasch et al., 2009). Relatedly, these basic muscle contractions and/or repetitive movements may induce muscular fatigue, which can also induce cortical excitability changes in the limb(s) involved in the contraction or movement (Ranieri and Di Lazzaro, 2012; Taylor and

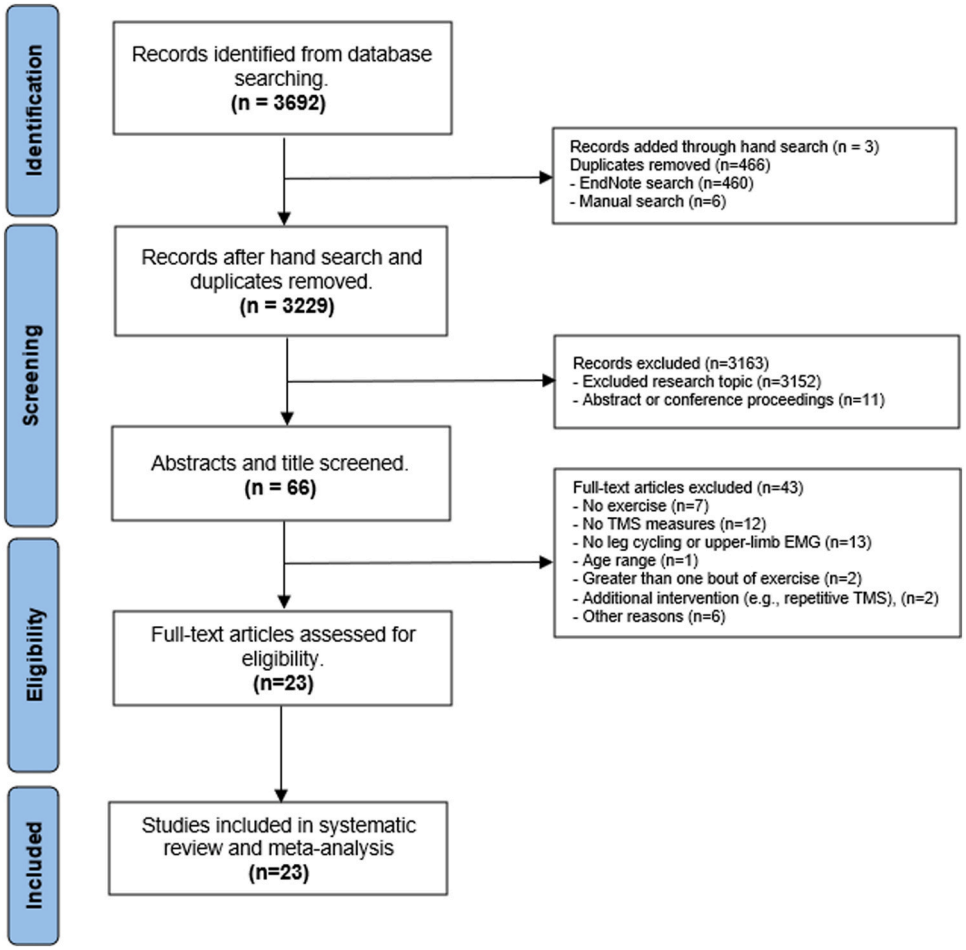

Fig. 1. : PRISMA flowchart of the systematic review process. The blue squares represent the key stages of the search. The flowchart represents the sequential steps for the selection and screening of studies according to inclusion criteria.

Gandevia, 2001). Thus, lower-limb cycling exercise enhances the likelihood of a robust and whole-body cardiorespiratory aerobic response, while also controlling for the potential confounding effects of repeated muscle contractions, movements and fatigue on cortical excitability changes. This enhances the ability to assess the effects of aerobic exercise on cortical excitability.

2.3.3. Control

No restrictions were placed on the presence or absence of a control condition/group in the study. As our analysis consisted of assessing potential changes pre and post AAE, we considered the pre-AAE measures as a control measure.

2.3.4. Outcome

Studies using TMS to measure neurophysiological changes close in time to cycling AAE were included. Studies using repetitive TMS were not included. TMS-based neurophysiological measurements considered for data extraction were the following: resting motor threshold, active motor threshold, MEP data, SICI, LICI, SICF, ICF, contralateral silent period, ipsilateral silent period, short-latency afferent inhibition, long-latency afferent inhibition, and cerebellar brain inhibition.

2.3.5. Studies

Except for cross-sectional studies, no other restriction on study design was considered.

2.4. Data extraction and methodological quality assessment

Following article screening, data were extracted to a custom spreadsheet using the text, figures (using *Graph Grabber*) and tables of each included study. Extraction was performed by one author (LY) and cross-checked entirely by another author (NH). The extracted information (Table 2) included: (1) authors and publication year; (2) participant characteristics (sample size, gender and age); (3) exercise intervention characteristics (duration, type, intensity and the method used to prescribe it); and (4) the TMS neurophysiological assessment characteristics (time of measure, measured variables and outcome).

The Cochrane risk of bias tool (RoB 2.0) was used to evaluate the methodological quality of the included studies (Higgins et al., 2019). This tool comprises five domains to assess the risk of bias in the studies: the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. Each of these domains is classified into one of three categories: "high risk," "some concerns," or "no risk." The overall risk of bias for each study is determined using the same categories. Notably, if a study has even a single domain assessed as having some concerns, the overall risk of bias for that study is also assessed as some concerns. The methodological quality of the included studies (Table 3) was assessed by one author (LY) and cross-checked entirely by another author (NH). In the event of a disagreement, a third reviewer (JN) was brought in to reach a consensus.

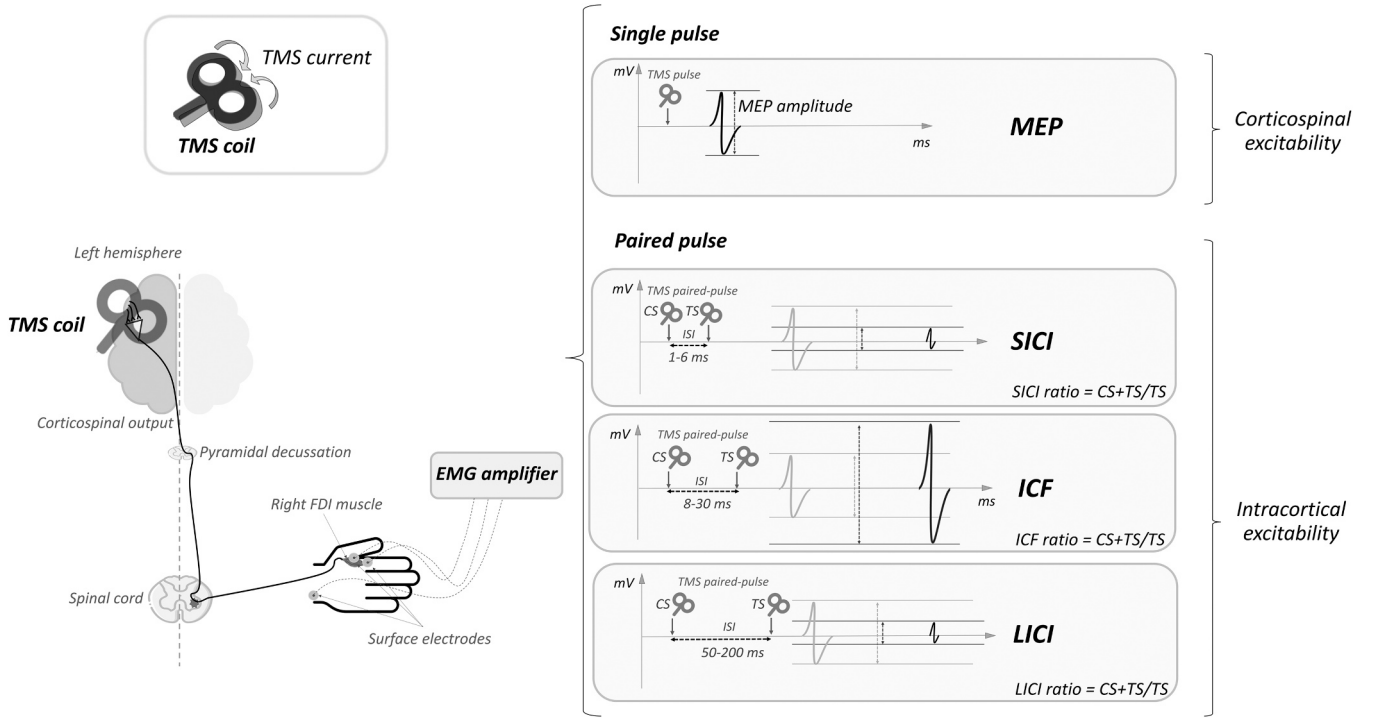

Fig. 2. : Figure showing the main measures included in the meta-analysis. TMS = transcranial magnetic stimulation. FDI = first dorsal interosseus. EMG = electromyography. MEP = motor evoked potential. SICI = short-interval intracortical inhibition. ICF = intracortical facilitation. LICI = long-interval intracortical inhibition. ISI = interstimulus interval. CS = conditioning stimulus. TS = test stimulus. CS + TS = paired-pulse with a first stimulus (CS) followed by a second stimulus (TS) separated by a pre-defined ISI. ms = milliseconds. mV = milliVolts.

Table 3
Risk of bias assessment of the included studies by Cochrane's Rob 2.0 tool.

Author, year	Randomisation Process	Deviation from intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall risk of bias
Andrews et al., (2020)	?	+	+	+	+	?
Brown et al., (2020)	+	+	+	+	+	+
El-Sayes et al., (2019)	?	+	+	+	+	?
El-Sayes et al., (2020)	?	+	+	+	+	?
Hendy et al., (2022)	?	+	+	?	+	?
Kuo et al., (2023)	?	+	+	+	+	?
Lulic et al., (2017)	+	+	+	+	+	+
MacDonald et al., (2019)	?	+	+	+	+	?
Mang et al., (2014)	?	+	+	+	+	?
Mang et al., (2016)	?	+	+	+	+	?
McDonnell et al., (2013)	?	+	+	+	+	?
Morris et al., (2020)	+	+	+	?	+	?
Mooney et al., (2016)	?	+	+	+	+	?
Neva et al., (2017)	?	+	+	+	+	?
Neva et al., (2021)	+	+	+	+	+	+
Nicolini et al., (2020)	?	+	+	+	+	?
Ostadan et al., (2016)	?	+	+	+	+	?
Singh et al., (2014)	?	+	+	+	+	?
Singh et al., (2016)	?	+	+	+	+	?
Smith et al., (2014)	?	+	+	+	+	?
Smith et al., (2018)	?	+	+	+	+	?
Stavrinos and Coxon, (2017)	+	+	+	?	+	?
Yamazaki et al., (2019)	?	+	+	+	+	?

+ refers to no risk of bias; ? refers to some concerns; - refers to high risk of bias

2.5. Main analyses and outcome measures

2.5.1. Main analyses

In our main analysis, we sought to determine the TMS-based measure of cortical excitability that was most consistently impacted by AAE. As different TMS measures of M1 excitability reflect unique underlying neurophysiological mechanisms, analysis was conducted for each measure separately.

2.5.2. Outcome measures

The neurophysiological measurements considered for data extraction were the following: resting motor threshold, active motor threshold, MEP data, SICI, LICI, SICF, ICF, contralateral silent period, ipsilateral silent period, short-latency afferent inhibition, long-latency afferent inhibition, and cerebellar brain inhibition. We performed a meta-analysis when measurements were assessed in at least four studies. As MEP changes were assessed differently throughout the studies, MEP data was extracted from peak-to-peak amplitudes, normalized MEP peak-to-peak amplitudes to $M_{max,}$ area under the recruitment curve (AUC) or linear slope of the recruitment curve / MEP recruitment curve slope. If multiple TMS intensities were used to assess MEPs, we prioritized data extraction and analysis of AUC or linear slope of the recruitment curve/ MEP recruitment curve, as these provide an assessment of overall corticospinal excitability (Brown et al., 2014; Chen et al., 2008; Neva et al., 2020). If these measures were not available and there were multiple intensities of single pulse TMS data collected in the study (e.g., 100–140 % resting motor threshold in 10 % increments) then 120 % or 130 % resting motor threshold was chosen. These two intensities have been shown to reflect the inflection point of the linear slope of the recruitment curve, and thus, are more easily able to measure potential changes before and after an intervention, like AAE (Rossini et al., 2015). This portion of the recruitment curve has been shown to induce the most significant exercise-related changes (Lulic et al., 2017). For SICI, data were extracted separately at 1 ms ($SICI_{1\ ms}$) and at 2–5 ms ($SICI_{2–5\ ms}$) interstimulus intervals (ISI) due to the known distinct mechanisms tested at different ISIs (Fisher et al., 2002; Stagg et al., 2011; Ziemann et al., 2015). For ICF and LICI, due to the small amount of available data (Pigott and Polanin, 2019), data were pooled to perform separate analyses with the different parameters as factors (e.g., ISI).

2.6. Moderator analyses

In addition to our main analyses, we defined moderators to examine mediating factors of AAE's impact on TMS-based measures of cortical excitability change. These moderating factors included: (i) *AAE intensity* and (ii) *time-window of post-AAE TMS assessment.*

We decided to examine AAE intensity since several studies indicated it is an important mediator of AAE-induced excitability change (Neva et al., 2022; Opie and Semmler, 2019; Singh and Staines, 2015), response to neuroplasticity inducing protocols (Andrews et al., 2020) and motor learning (Roig et al., 2012). Since variations may exist in the prescription of AAE intensity across different studies, we categorized AAE intensity into low, moderate, and high based on the American College of Sports Medicine (ACSM) guidelines (Liguori et al., 2021). Most studies used a percentage of age-predicted maximum heart rate (MHR) or heart rate reserve (HRR), while others used different parameters (e.g., peak power output achieved at a maximal graded exercise test), which allowed us to use the ASCM guidelines to categorize AAE intensities. Using the ACSM guidelines, we were able to categorise the exercise intensities used in the included studies into low (30–39 % HRR or 57–63 % MHR), moderate (40–59 % HRR or 64–76 % MHR) and high (60–89 % HRR and 77–95 % MHR).

The interest in the time-window of AAE effects on TMS-based measures of cortical excitability is important to understand the duration of effects (Lulic et al., 2017; Mooney et al., 2016; Neva et al., 2017; Smith et al., 2014). Due to the wide variety of *time-window of post-AAE TMS assessment*, in terms of frequency, duration and timing post-AAE, we defined three distinct time-windows post-AAE to pragmatically categorise the available data: 0–30 min post-AAE (post 1), 31–60 min post-AAE (post 2) and > 61 min post-AAE (post 3). These time windows permitted input of data from most studies. However, for two studies, it was necessary to average two post-AAE time points within one of our defined post-AAE time windows (Mooney et al., 2016; Smith et al., 2014). For all of the reasons listed above, this analysis was considered exploratory.

2.7. Statistical analysis

2.7.1. Main analyses

All statistical analyses were performed using R software (3.6.2; foundation for statistical computing, Vienna, Austria) and the packages *metafor, meta, dmetar*. Forest plots were generated using the R-package *metafor*. We input mean values (pre- to post-AAE) and standard deviation of each TMS-based measure of cortical excitability. Consequently, standardised mean differences (pre- to post- AAE) were calculated with 95 % confidence intervals (CIs) along with effect sizes. Anticipating the inclusion of studies with small sample sizes, we used Hedge's *g* as a measure of effect size (Hedges, 1981) and by convention, values of 0.2, 0.5, and 0.8 represent small, medium, and large effect size respectively. Overall estimates were computed using a random effect model with the DL (DerSimonian and Laird) method of estimation. When we included studies with multiple arms, we conducted multi-level mixed effects meta-analyses to account for the nested structure of effect sizes within groups and studies. Between-study effect sizes were calculated using the I^2 statistic and by convention, values ranging from 0 % to 40 % indicate low heterogeneity between studies, 30–60 % signify moderate heterogeneity, 50–90 % represent substantial heterogeneity, and 75–100 % denote considerable heterogeneity (Higgins et al., 2003). Due to the repeated measures design of the included studies, a correlation coefficient of 0.5 was used between pre- and post-AAE values. Significance level was set at $p < .05$ for all statistical tests.

2.7.2. Moderator analysis

Analyses of moderators were conducted to examine whether (i) AAE intensity *(low- vs. moderate- vs. high- intensity AAE)* and (ii) time-window of post-AAE TMS assessment *(post 1- vs. post 2-, vs. post 3- AAE)*, mediated the effects. Similarly to our main analysis, heterogeneity across subgroup effects was evaluated using I^2 statistics. To identify potential subgroup differences, a meta-regression analysis was then performed on random effects models for all AAE intensities and for time points post-AAE. The meta-regression was parameterized through the inclusion of random effects. Only TMS-based neurophysiological measures with two or more studies were considered for meta-analysis. If our main analysis revealed a significant effect for a TMS-based measure of cortical excitability, follow-up moderator analysis distinguishing our predefined AAE intensities (low, moderate, high) were performed. Similarly, follow-up moderator analysis on the three predefined time windows post-AAE were performed if the main analysis revealed a significant effect. The potential influence of publication bias was assessed through visual inspection of funnel plots. Additionally, a sensitivity analysis was conducted using the Cochrane risk of bias tool to assess study quality.

3. Results

3.1. Trial flow

After our systematic database search, a total of 3692 articles were found and 3229 articles remained after hand search and duplicate removal using Endnote (Clarivate, 2024). Following title and abstract screening, 66 studies remained, and 23 articles remained after full-text screening. Finally, these 23 articles were considered eligible and were included in the meta-analysis. The PRISMA flowchart of the systematic review process is shown in Fig. 1.

3.2. Study characteristics

A detailed summary of the characteristics of each study is provided in Table 2. Concerning the main neurophysiological measures, corticospinal excitability (assessed via MEP data) was measured in 21 studies using various methodologies. Intracortical inhibition was measured in 13 studies, with 13 including SICI (Andrews et al., 2020; El-Sayes et al., 2019; Hendy et al., 2022; Kuo et al., 2023; Lulic et al., 2017; Mooney

et al., 2016; Morris et al., 2020; Neva et al., 2021; Nicolini et al., 2020; Singh et al., 2014; Smith et al., 2014; Stavrinos and Coxon, 2017; Yamazaki et al., 2019) and 6 including LICI (Andrews et al., 2020; Mooney et al., 2016; Morris et al., 2020; Singh et al., 2014; Stavrinos and Coxon, 2017; Yamazaki et al., 2019). Intracortical facilitation was measured in 7 studies, all of which measuring ICF (Kuo et al., 2023; Lulic et al., 2017; Morris et al., 2020; Nicolini et al., 2020; Singh et al., 2014; Yamazaki et al., 2019) and 3 measuring SICF (Lulic et al., 2017; Neva et al., 2017; Yamazaki et al., 2019). Assessments of the silent period was measured in 2 studies, with both studies including contralateral silent period (Mooney et al., 2016; Neva et al., 2017) and 1 study including ipsilateral silent period (Neva et al., 2017). Finally, paired-pulse and dual-site TMS studies assessed inhibitory connectivity to M1 from other regions, with 2 studies measuring connectivity from the primary somatosensory cortex using short-latency afferent inhibition (Brown et al., 2020; Yamazaki et al., 2019), 1 study using long-latency afferent inhibition (Brown et al., 2020) and 1 study measuring cerebellar inhibition (Mang et al., 2016).

In terms of AAE intensity, all studies except one aligned with the ACSM guidelines (Liguori et al., 2021). Morris et al. (2020) classified the intensity of their exercise as low intensity with a prescription of exercise of 40–60 % of age-predicted heart rate reserve. However, according to ACSM guidelines (Liguori et al., 2021) this intensity is classified as moderate. Consequently, this study was included in the moderate-AAE intensity group. Ten studies prescribed high-intensity AAE (Andrews et al., 2020; El-Sayes et al., 2020; Hendy et al., 2022; Mang et al., 2016, 2014; Nicolini et al., 2020; Ostadan et al., 2016; Smith et al., 2014, 2018; Stavrinos and Coxon, 2017), 15 studies prescribed moderate-intensity AAE (Andrews et al., 2020; Brown et al., 2020; El-Sayes et al., 2020, 2019; Kuo et al., 2023; Lulic et al., 2017; MacDonald et al., 2019; McDonnell et al., 2013; Mooney et al., 2016; Morris et al., 2020; Neva et al., 2017; Neva et al., 2021; Singh et al., 2016; Singh et al., 2014; Smith et al., 2014) and 3 studies prescribed low-intensity AAE (MacDonald et al., 2019; McDonnell et al., 2013; Yamazaki et al., 2019). In terms of time-window post-AAE measurement of TMS-based cortical excitability, data from 21 studies fell within the 0–30 min post-AAE time window, data from 4 studies fell within the 31–60 min time window post-AAE, and data from 2 studies reported data in the > 60 min time window post-AAE.

3.3. Risk of bias and methodological quality

The Cochrane risk of bias tool was used to assess the methodological quality of the studies (Table 3). According to this tool, the majority of our included studies (K = 20) had an overall score of risk of bias rated as "some concerns". This score primarily stemmed from inadequate details regarding randomization procedures as the method used for randomization was not reported. It is important to highlight that randomization procedures used in TMS-based studies like those included in this meta-analysis are very rare and are often not feasible. Three studies had an overall risk of bias rated as "no risk of bias". Concerning publication bias, visual inspection of funnel plots showed no reporting bias for the main TMS neurophysiological measures as studies were distributed in a symmetrical way (see supplementary material).

3.4. Main analysis: effect of acute aerobic exercise on TMS-based neurophysiological measures

A summary of the results of our main analysis is shown in Table 4. We found decreased $SICI_{2–5\ ms}$ with a small effect size (g = 0.27, 95 % CI [0.16; 0.38], p <.0001; Fig. 3) and low heterogeneity (I^2 = 16 %). Increased corticospinal excitability (CSE) with a trivial effect size (g = 0.13, 95 % CI [0.01; 0.26], p =.05; Fig. 4) and moderate heterogeneity (I^2 = 50 %) was found. Decreased ICF with a trivial effect size (g = −0.08, 95 % CI [-0.36; 0.21], p =.59; Fig. 5) and moderate heterogeneity (I^2 = 72 %) was observed. A trivial size was found for both increased RMT (g = 0.05, 95 % CI [-0.11; 0.21], p =.56) and increased LICI (g = 0.06, 95 % CI [-0.11; 0.24], p =.48; Fig. 6)

3.5. Moderator analysis of AAE intensity and time-window post-AAE on TMS-based neurophysiological measures

A summary of the results of our meta-regression analysis is shown in Table 5. For SICI, we found decreased $SICI_{2–5\ ms}$ at moderate- (g = 0.18, 95 % CI [0.05; 0.31], p <.01) and high- (g = 0.49, 95 % CI [0.27; 0.71], p <.0001) intensity AAE with trivial and medium effect sizes respectively, but not at low- (g = 0.34, 95 % CI [-0.04; 0.72], p =.08) intensity AAE. Additionally, a small effect was observed for decreased $SICI_{2–5\ ms}$ (g = 0.31, 95 % CI [0.19; 0.44], p <.01) in the 0–30 min post-AAE window, but not for both the 31–60 min (g = 0.18, 95 % CI [-0.09; 0.46], p =.20) and the > 61 min (g = −0.20, 95 % CI [-0.72; 0.32], p =.45) post-AAE time windows. For the observed increase in CSE, the meta-regression analysis revealed that high-intensity AAE showed a small effect (g = 0.28, 95 % CI [0.07; 0.48], p <.01), which was not found for moderate- (g = 0.07, 95 % CI [-0.09; 0.23], p =.41), or low- (g = −0.07, 95 % CI [-0.47; 0.33], p =.72), intensity AAE. Concerning decreased ICF, small effect sizes were observed for high- (g = −0.22, 95 % CI [-0.86; 0.42], p =.51), and moderate- (g = 0.10, 95 % CI [-0.25; 0.46], p =.56) intensity AAE, respectively. For increased resting motor threshold, trivial effect sizes were observed for high- (g = 0.02, 95 % CI [-0.28; 0.33], p =.88), moderate- (g = 0.06, 95 % CI [-0.20; 0.31], p =.67) and low- (g = 0.09, 95 % CI [-0.45; 0.65], p =.73) intensity AAE. For increased LICI, a trivial effect was observed for high- (g = 0.03, 95 % CI [-0.35; 0.42], p =.86), moderate- (g = 0.06, 95 % CI [-0.21; 0.34], p =.65) and low- (g = 0.11, 95 % CI [-0.29; 0.51], p =.59) intensity AAE.

4. Discussion

We synthesized data on the effects of AAE on neurophysiological measures of excitability assessed by TMS. Data from 23 studies, including 474 participants, were used in our meta-analysis. Our main analysis demonstrated a consistent decrease in intracortical inhibition (measured with $SICI_{2–5\ ms}$) following AAE. Moreover, moderator analyses demonstrated decreased $SICI_{2–5\ ms}$ for both moderate- and high-

Table 4
Summary of effect size.

Outcome	K	k	N	Meta-analysis			Heterogeneity		
				Effect size	95 % CI	P-value	Q value	P- value	I^2
RMT	7	9	130	0.05	-0.11; 0.21	.56	9.2	.33	12.7
CSE	21	28	430	0.13	0.01; 0.26	.05	53.9	.001	49.9
$SICI_{2–5\ ms}$	13	23	280	**0.27**	**0.16; 0.38**	**<.0001**	**26.2**	**<.001**	**15.9**
ICF	7	11	130	-0.08	-0.36; 0.21	.59	36.04	<.001	72.2
LICI	6	9	95	0.06	-0.11; 0.24	.48	8.4	.40	22.0

Significant effect sizes are shown in bold. K = number of studies evaluating the neurophysiological measure; k = number of assessments included in the analysis; N = number of participants. 95 % CI = 95 % confidence interval. RMT = resting motor threshold; CSE = corticospinal excitability; SICI = short-interval intracortical inhibition; ICF = intracortical facilitation; LICI = long-interval intracortical inhibition; 2–5 ms refer to the different inter-stimulus intervals.

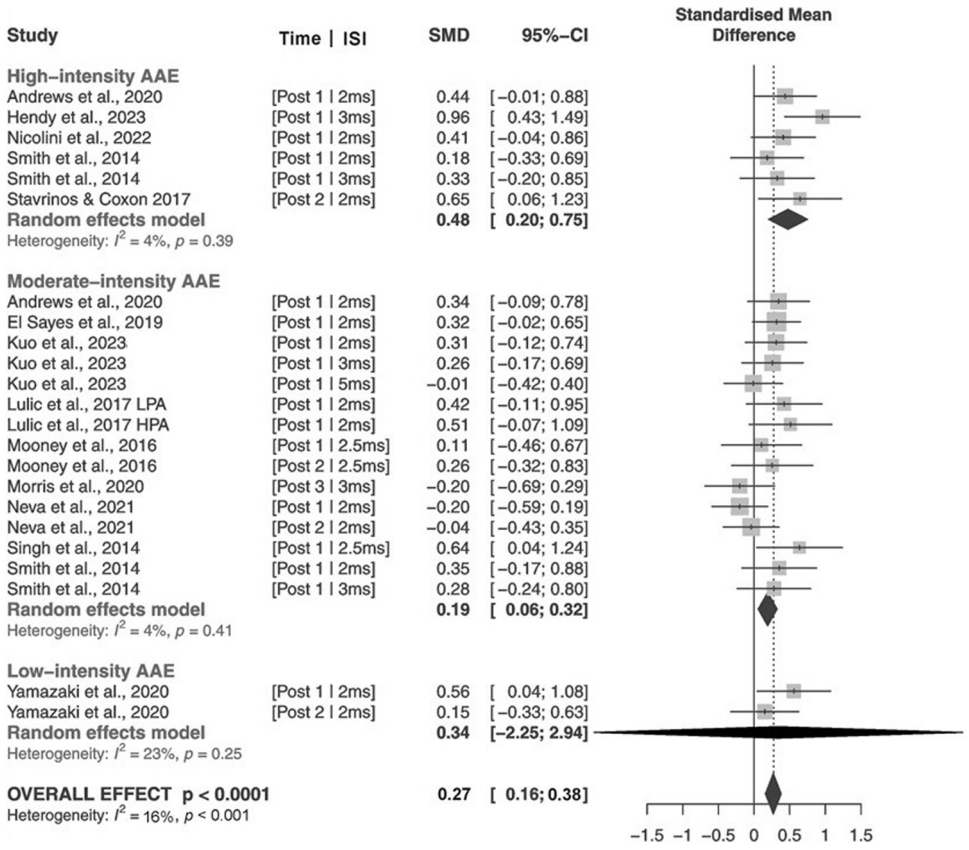

Fig. 3. : Forest plot showing the effect of acute aerobic exercise (AAE) on short-interval intracortical inhibition ($SICI_{2–5\ ms}$). AAE = acute aerobic exercise. LPA = low physical activity level; HPA = high physical activity level. Time refers to time window of TMS assessment; Post 1 = 0–30 min post-AAE; Post 2 = 31–60 min post-AAE; Post 3 = > 61 min post-AAE. ISI refers to inter-stimulus intervals. SMD = standardised mean difference; CI = confidence interval.

intensity AAE, but not for low-intensity AAE. These effects persist for up to 30 minutes post AAE. Additionally, our moderator analysis showed increased corticospinal excitability only at high intensity AAE. It is important to note that there was relatively little data for studies using low-intensity AAE, which may have influenced the moderator analysis for this intensity. Similarly, few studies included measurements during our 31–60 min and > 61 min post-AAE time-windows. Thus, the current results on the duration of effects should be interpreted with caution.

4.1. *Effect of acute aerobic exercise on intracortical inhibition*

As expected, we found evidence for a consistent (i.e., moderate heterogeneity between studies) decrease in SICI following AAE. Our expectation was based on most studies in the field demonstrating significantly decreased SICI, regardless of the exercise intensity or characteristics of the population (e.g., high or low physical activity (Lulic et al., 2017). It is important to note that some studies found no effect of AAE on SICI (Mooney et al., 2016; Morris et al., 2020; Neva et al., 2021; Nicolini et al., 2020), which may have contributed to our observed small effect size. Several potential mechanisms may underpin the reduction in SICI observed following AAE. In the networks of cortical inhibition, GABA (γ-aminobutyric acid), an inhibitory neurotransmitter, can affect several receptors, such as $GABA_A$ and $GABA_B$ receptors. $GABA_A$ receptors are ligand-gated chloride channels thought to mediate SICI through fast-acting synaptic transmission (Chen et al., 2014). It has been shown that synaptic inhibition modulated by $GABA_A$ is reflected by SICI in M1 through the projection of intracortical interneurons onto corticospinal output neurons (Di Lazzaro et al., 1998; Hanajima et al., 1998). It is important to note that the observed effect was specifically for $SICI_{2–5\ ms}$ and not $SICI_{1\ ms}$. $SICI_{2–5\ ms}$ is known to reflect $GABA_A$-receptor related inhibition and synaptic transmission (Ziemann et al., 2015), while $SICI_{1\ ms}$ has been shown to reflect extracellular GABA-related activity and/or refractory mechanisms of the axon due to the short interval of stimuli (Fisher et al., 2002; Stagg et al., 2011). The current findings support the notion that AAE specifically alters mechanisms underlying $SICI_{2–5\ ms}$, i.e., $GABA_A$-receptor related synaptic inhibition. It is possible that $GABA_A$-receptor related inhibition underpins the exercise-enhanced response to neuroplasticity-inducing repetitive TMS protocols (Andrews et al., 2020; Mang et al., 2014; Singh et al., 2014) and motor learning (Mang et al., 2014; Neva et al., 2019; Stavrinos and Coxon, 2017). To date, no study has specifically shown that $GABA_A$-receptor related inhibition changes via SICI is related to these AAE-induced changes. It will be necessary for future research to explore this specific question.

In addition to $GABA_A$-receptor related inhibition being modulated by AAE, there are likely other mechanisms that may underlie or interact with decreased SICI. This includes the influence of brain-derived neurotrophic factor (BDNF) secretion, which is known to be released after even a brief bout of aerobic exercise (Knaepen et al., 2010; Mang et al., 2014; McDonnell et al., 2013; Rojas Vega et al., 2006; Singh et al., 2014; Skriver et al., 2014). Interestingly, it has been shown that BDNF can suppress the post-synaptic receptors of GABAergic inhibition in animal models (Tanaka et al., 1997). High-intensity AAE induces the highest levels of BDNF in the brain (compared to low- and moderate-intensity exercise), which appears to reduce intracortical inhibition mediated by $GABA_A$ receptors (Brünig et al., 2001). Greater levels of BDNF induced by relatively higher intensity exercise could partly explain the greater reduction in $SICI_{2–5\ ms}$ compared with lower intensities of AAE. Since the specific findings of our meta-regression found decreased SICI at both moderate- and high-intensities of AAE, it is possible that BDNF could play a role in, or interact with, the decreased $GABA_A$ receptor-related activity at both AAE intensities. However, this is

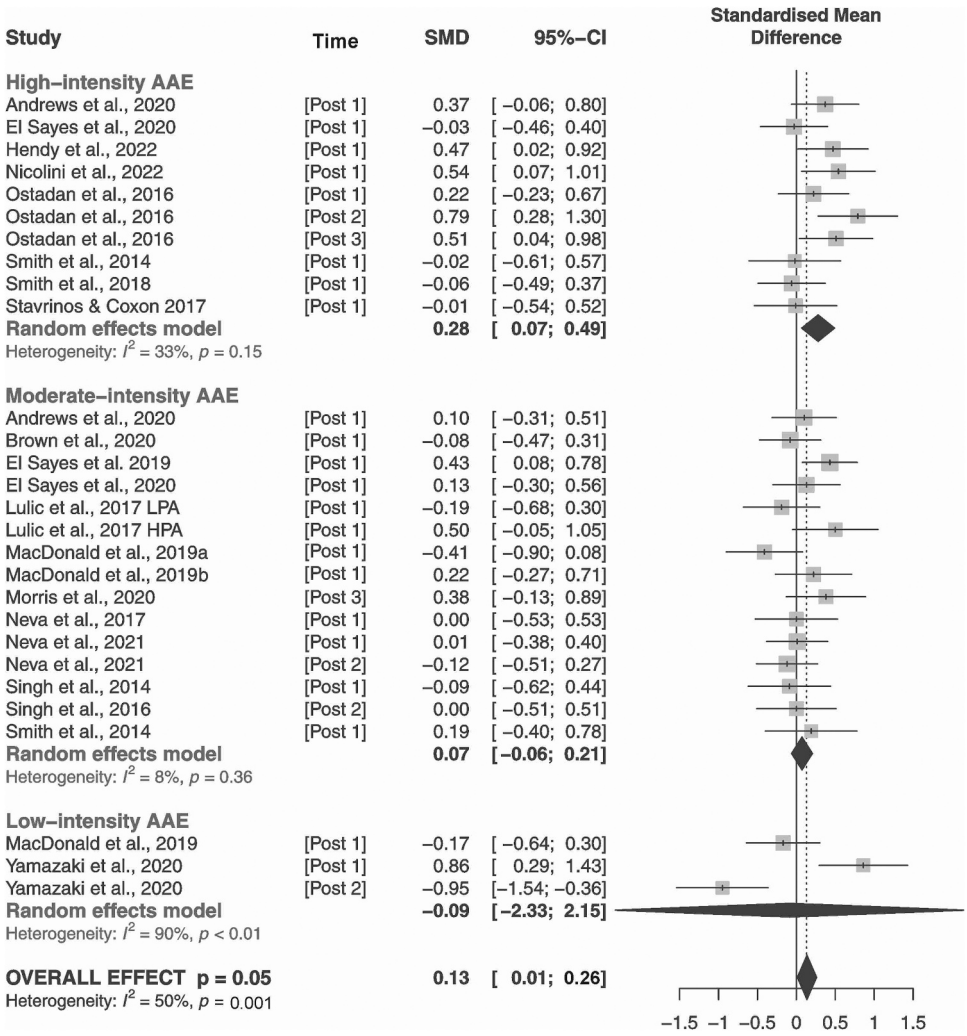

Fig. 4. : Forest plot showing the effect of acute aerobic exercise (AAE) on corticospinal excitability (CSE). AAE = acute aerobic exercise. LPA = low physical activity level; HPA = high physical activity level. Time refers to time window of TMS assessment; Post 1 = 0–30 min post-AAE; Post 2 = 31–60 min post-AAE; Post 3 = > 61 min post-AAE. a and b are used since the same study (MacDonald et al., 2019) used moderate intensity twice with different parameters of intervention; a = 40 % Heart Rate Reserve (HRR), b = 50 % HRR. SMD = standardised mean difference; CI = confidence interval.

speculative since the current meta-analysis did not specifically investigate the AAE-induced changes in BDNF nor $GABA_A$ receptor-related activity in the included articles of this study.

Dopamine release or activation may play a role in the AAE-induced decrease in SICI observed in our meta-analysis. Dopamine plays an important role in the regulation of M1 excitability as measured by TMS (i.e., SICI) (Curtin et al., 2023; Tritsch and Sabatini, 2012), and dopamine production is responsive to exercise. High intensities of AAE can induce higher levels of dopamine in the brain (Greenwood, 2019; Mooney et al., 2019). Previous studies indicate increased dopamine release contributes to reduced $GABA_A$ receptor activity (Flores-Hernandez et al., 2000), as well as increased N-methyl--D-aspartate (NMDA) and glutamate receptor activity (Chen et al., 2004). Consequently, the higher levels of dopamine induced by high- and moderate-intensity exercise may also contribute to the reduction in $SICI_{2–5\ ms}$ compared with lower-intensity exercise as found in the current study. Also, dopamine D2 receptor blockade eliminates decreased SICI following AAE in young adults (Curtin et al., 2023). Since blockade of the D2 receptor removes the AAE-induced decreased SICI that is commonly found, it is entirely possible that the dopamine D2 receptor activity plays a critical role in decreased SICI following AAE found in this meta-analysis. Thus, dopamine release or activation may be an underlying mechanism supporting or interacting with the current findings of decreased intracortical inhibition (i.e., SICI) following acute exercise. Future research will be necessary to understand if the AAE-induced effect of decreased SICI depends upon or interacts with the dopamine D2 receptor, and the physiological changes that occur with the D2 receptor after AAE.

Regardless of the specific underlying mechanisms and interaction between other underlying mechanisms, GABAergic disinhibition appears to be a consistent effect following moderate and high AAE intensities. Consequently, this finding presents a promising avenue for the use of acute aerobic exercise in both behavioral and clinical contexts. This includes enhancing motor performance, motor learning, as well as informing rehabilitation practices. For instance, several studies have shown that $SICI_{2–5\ ms}$ is decreased following the practice of motor learning and sequence learning tasks (Berghuis et al., 2015; Cirillo et al., 2011; Coxon et al., 2014; Perez et al., 2004). Additionally, $SICI_{2–5\ ms}$ is known to be a critical mechanism supporting fine motor control, particularly preventing unwanted muscle activation and assisting with fractionated finger movement (Rosenkranz and Rothwell, 2004; Stinear and Byblow, 2003; Zoghi et al., 2003). Future research should be performed to further understand the exercise parameters (e.g., intensity, duration, type), TMS parameters and interacting underlying mechanisms contributing to the observed effects.

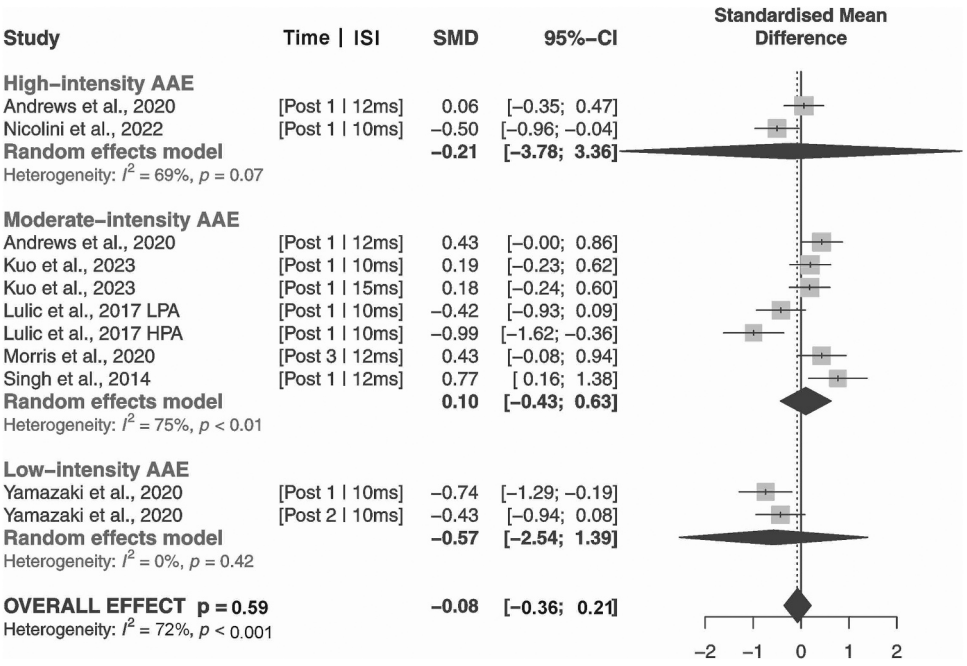

Fig. 5. : Forest plot showing the effect of acute aerobic exercise (AAE) on intracortical facilitation (ICF). AAE = acute aerobic exercise. LPA = low physical activity level; HPA = high physical activity level. Time refers to time window of TMS assessment; Post 1 = 0–30 min post-AAE; Post 2 = 31–60 min post-AAE; Post 3 = > 61 min post-AAE; ISI refers to inter-stimulus intervals. SMD = standardised mean difference; CI = confidence interval.

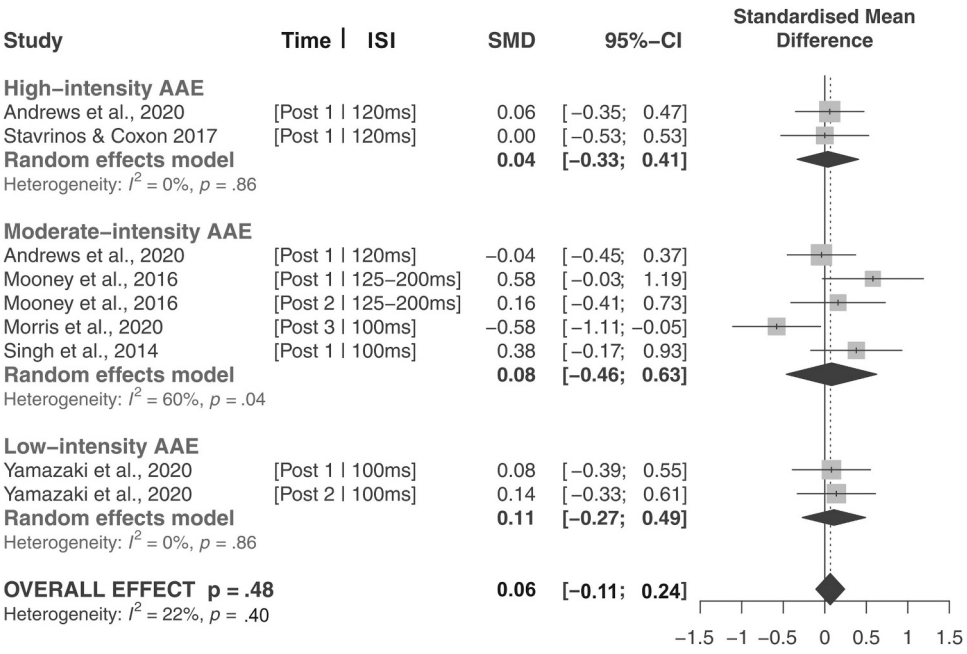

Fig. 6. : Forest plot showing the effect of acute aerobic exercise (AAE) on long-interval intracortical inhibition (LICI). AAE = acute aerobic exercise. Time refers to time window of TMS assessment; Post 1 = 0–30 min post-AAE; Post 2 = 31–60 min post-AAE; Post 3 = > 61 min post-AAE; ISI refers to inter-stimulus intervals. SMD = standardised mean difference; CI = confidence interval.

4.2. Effect of acute aerobic exercise on corticospinal excitability

Our main meta-analysis demonstrated an increased corticospinal excitability post-AAE across all studies as measured by MEP data, but with a trivial effect size. Interestingly, our moderator analysis showed that high intensity AAE induced an increased corticospinal excitability with a small effect size, whereas this effect was not present for moderate or low intensity AAE. Overall, these results suggest that only AAE at high intensity is sufficient to enhance measures of corticospinal excitability. Although we expected our meta-analysis to reveal no change in corticospinal excitability following AAE, the current findings could be at least partly related to the AAE parameters (exercise intensity, type, and duration) and the physical activity or cardiorespiratory fitness levels of participants.

To date, the impact of AAE on corticospinal excitability changes in young adults is variable. Some studies showed increased corticospinal excitability (El-Sayes et al., 2019; Hendy et al., 2022; Lulic et al., 2017; MacDonald et al., 2019; Nicolini et al., 2020; Ostadan et al., 2016),

Table 5
Estimates from the meta-regression analyses.

Moderators	Estimate	SE	95 % CI	P-value
High-Intensity AAE				
RMT	0.02	0.16	-0.28; 0.33	.88
CSE	**0.28**	**0.10**	**0.07; 0.48**	**<.01**
$SICI_{2–5\ ms}$	**0.49**	**0.11**	**0.27; 0.71**	**<.0001**
ICF	-0.22	0.33	-0.86; 0.42	.51
LICI	0.03	0.19	-0.35; 0.42	.86
Moderate-Intensity AAE				
RMT	0.06	0.13	-0.20; 0.31	.67
CSE	0.07	0.08	-0.09; 0.23	.41
$SICI_{2–5\ ms}$	**0.18**	**0.06**	**0.05; 0.31**	**<.01**
ICF	0.10	0.18	-0.25; 0.46	.56
LICI	0.06	0.14	-0.21; 0.34	.65
Low-Intensity AAE				
RMT	0.09	0.28	-0.45; 0.65	.73
CSE	-0.07	0.20	-0.47; 0.33	.72
$SICI_{2–5\ ms}$	0.34	0.19	-0.04; 0.72	.08
ICF	-0.57	0.35	-1.26; 0.10	.09
LICI	0.11	0.21	-0.29; 0.51	.59
Post 1				
CSE	0.13	0.07	-0.01; 0.27	.06
$SICI_{2–5\ ms}$	**0.31**	**0.06**	**0.19; 0.44**	**<.01**
Post 2				
CSE	-0.04	0.17	-0.39; 0.29	.79
$SICI_{2–5\ ms}$	0.18	0.14	-0.09; 0.46	.20
Post 3				
CSE	0.45	0.24	-0.03; 0.92	.07
$SICI_{2–5\ ms}$	-0.20	0.26	-0.72; 0.32	.45

Significant estimates are shown in bold. SE = standard errors. 95 % CI = 95 % confidence intervals. RMT = resting motor threshold; CSE = corticospinal excitability; SICI = short-interval intracortical inhibition; ICF = intracortical facilitation; LICI = long-interval intracortical inhibition; AAE = acute aerobic exercise; Post 1 = 0–30 min post-exercise; Post 2 = 31–60 min post-exercise; Post 3 = > 60 min post-exercise; 2–5 ms refer to the different inter-stimulus intervals.

whereas the majority showed no change (Andrews et al., 2020; Brown et al., 2020; El-Sayes et al., 2020; Kuo et al., 2023; Mang et al., 2014; McDonnell et al., 2013; Morris et al., 2020; Neva et al., 2017, 2021; Singh et al., 2016, 2014; Smith et al., 2014, 2018; Stavrinos and Coxon, 2017; Yamazaki et al., 2019) in response to AAE. Based on our finding that high intensity AAE significantly increases corticospinal excitability, it is likely that the potential underlying factors contributing to these findings requires a nuanced examination of the results. For instance, AAE parameters like intensity, along with a combination of others such as type and duration, may be important factors in determining the effect of AAE on corticospinal excitability of the non-exercised upper-limb muscles. Many reports have demonstrated that continuous low- or moderate-intensity AAE does not impact corticospinal excitability (Andrews et al., 2020; Brown et al., 2020; El-Sayes et al., 2020; Kuo et al., 2023; McDonnell et al., 2013; Morris et al., 2020; Neva et al., 2017, 2021; Singh et al., 2016, 2014; Smith et al., 2014; Yamazaki et al., 2019). However, others have found that high-intensity interval (HIIT) exercise increased corticospinal excitability (Hendy et al., 2022; Nicolini et al., 2020; Ostadan et al., 2016). Of note, it is possible that the higher level of HIIT intensity (e.g., 105–125 % VO_{2peak}) in these previous studies played an important factor in the exercise-enhanced corticospinal excitability observed (Hendy et al., 2022; Nicolini et al., 2020; Ostadan et al., 2016). Sufficiently high AAE intensities may be necessary to induce changes in corticospinal excitability. Of course, it is still important to keep in mind that other studies have reported no change after HIIT exercise (Andrews et al., 2020; El-Sayes et al., 2020; Mang et al., 2014; Stavrinos and Coxon, 2017). Moreover, moderate-intensity continuous exercise has been found to similarly increase corticospinal excitability (El-Sayes et al., 2019; Lulic et al., 2017; MacDonald et al., 2019). Thus, it appears that AAE intensity (as well as type and duration) are likely important factors when considering the impact on corticospinal excitability change. Importantly, in all three of these studies mentioned above (Hendy et al., 2022; Nicolini et al., 2020; Ostadan et al., 2016), the participants were categorized as sedentary (e.g., according to IPAQ or VO_{2peak} scores). Thus, it also appears that group-level exercise habits may be an important determinant of the impact of AAE on corticospinal excitability.

It is possible that levels of physical activity and/or cardiorespiratory fitness among participants played an important role in certain studies that demonstrated increased corticospinal excitability post-AAE (Hendy et al., 2022; Nicolini et al., 2020; Ostadan et al., 2016). For instance, although the standardized mean difference of studies within our meta-regression were mixed (i.e., some showing increasing corticospinal excitability, others showing no change), those studies that show increased corticospinal excitability following this high-intensity AAE included participants categorized as having low levels of physical activity (i.e., sedentary) and/or relatively lower physical fitness (Hendy et al., 2022; Nicolini et al., 2020; Ostadan et al., 2016). Hendy et al. (2022) and Nicolini et al. (2020) specifically recruited participants that were classified as sedentary (i.e., < 60 or 150 minutes of structured physical activity per week, respectively) (Hendy et al., 2022; Nicolini et al., 2020). Ostadan et al., (2016) reported that the average VO_{2peak} of participants was 38 mL/kg/min (Ostadan et al., 2016), which can be classified as sedentary or non-active (Peel et al., 2014). Thus, it is possible that those who are physically inactive or with relatively lower cardiorespiratory fitness levels have greater potential for increased corticospinal excitability following high intensity AAE compared to those who are more physically active. Supporting this, in other studies that found no change post-AAE, participants were physically active (Andrews et al., 2020; El-Sayes et al., 2020; Mang et al., 2014; Stavrinos and Coxon, 2017). Thus, physical activity and cardiorespiratory fitness levels may play an important role in the impact of AAE on corticospinal excitability and could have influenced the current findings. Future research in which the physical activity and cardiorespiratory fitness levels of the study participants is considered and/or controlled for is necessary to further understand their influence on AAE-induced changes to corticospinal excitability.

Finally, increase in blood lactate following high-intensity AAE may have contributed to our meta-regression findings of increased corticospinal excitability. Higher levels of blood lactate appear to be associated with increased brain use of lactate as a fuel source (Schurr, 2014; Xue et al., 2022), which increases with increasing exercise intensity (Xue et al., 2022). Lactate appears to be involved in various signaling cascades of mechanisms like BDNF (Fernández-Rodríguez et al., 2022) and glutamate (Basso and Suzuki, 2017). Low-intensity AAE does not induce the same lactate accumulation (Nordheim and Vøllestad, 1990). Therefore, accumulation of blood lactate could be a potential explanation for the effect of high-intensity AAE on corticospinal excitability.

4.3. Lack of significant changes in LICI and ICF

We observed trivial changes in resting motor threshold, ICF and LICI following AAE with large confidence intervals. Although not surprising, it is valuable to consider the potential explanations for these findings. One reason could be that there is simply a lack of sufficient data to observe any consistent effect. Specifically, there were only seven studies that measured resting motor threshold, six studies that measured LICI and seven studies that measured ICF. We did not perform a meta-analysis for active motor threshold, short-interval intracortical facilitation, short-afferent inhibition, long-afferent inhibition, ipsilateral silent period, and contralateral silent period due to the insufficient number of studies evaluating these measures. With more data on these measures, the impact of AAE on these M1 intracortical circuits could be assessed more effectively.

Although we found an effect of $GABA_A$-receptor related inhibition, as measured by SICI, we did not find an effect with the related $GABA_B$-receptor inhibition as measured by LICI. LICI interacts with, yet is distinct from, mechanisms underlying SICI ($GABA_A$ neurotransmission),

due to the mediation of $GABA_B$ receptor related inhibition, which couples with G-protein complexes to activate downstream potassium ion channels (McDonnell et al., 2006). Additionally, neural circuits underlying LICI are known to have higher excitability thresholds compared to SICI, which may contribute to the lack of consistent effects observed after AAE (Brown et al., 2014; Chen et al., 2008). While six studies measured LICI following AAE, only two studies showed either a significant decrease, or a trend for a decrease in LICI. Thus, it is not necessarily surprising that LICI does not change similarly to SICI following AAE.

The mechanisms underlying ICF are unclear, but may be mediated by glutamatergic interneurons, NMDA receptors, as well as potential I-wave facilitation (Liepert et al., 1997; Ziemann et al., 1998). Due to the lack of certainty of the underlying mechanisms of ICF, it is difficult to explain the inconsistent effects reported across studies. Another factor may be the difference in interstimulus intervals when assessing ICF across studies, with a range of 10–15 ms (Lazzaro et al., 2006). Although this is within the range of interstimulus intervals typically used to test ICF, there could be subtle differences in mechanisms and interneuron pools recruited within the different interstimulus intervals that led to the inconsistent findings (Kujirai et al., 1993). Further research is required to understand the specific factors that contribute to the lack of effect in these M1 intracortical circuits, such as exercise (e.g., AAE intensity, duration and type) and TMS (e.g., interstimulus interval, stimulus intensities) parameters.

4.4. Limitations

We were able to bring together multiple sets of data with vastly different TMS parameters, but the synthesis of these different TMS parameters can present some limitations to the analyses and interpretations of data. For instance, some studies measured corticospinal excitability by assessing raw peak-to-peak MEP amplitudes of one stimulus intensity, while other studies assessed multiple stimulus intensities (e.g., 100 %, 110 %, 120 %, 130 % of resting motor threshold, etc.). Some studies normalized the MEP amplitude to the maximal M-wave elicited post-AAE. Also, several studies made certain calculations of MEP amplitudes at multiple intensities, such as determining the area under the curve or linear slope of the recruitment curve to give an overall sense of corticospinal excitability. The current results are an amalgamation of all types of MEP data so that we could have an overall sense of the AAE-induced changes to corticospinal excitability. It is possible that certain studies are over or under-represented due to the pragmatic method by which we extracted MEP data (see methods). Therefore, the current results on AAE-induced changes to corticospinal excitability should be interpreted with this in mind.

AAE intervention variability is worth noting. There were very few studies using low-intensity AAE (as evidenced by our larger confidence intervals for low-intensity AAE). Thus, the non-significant effect of low-intensity AAE observed in our results might be due to insufficient data. Similarly, few studies had data beyond our first post-AAE time window (0–30 min). Therefore, results regarding duration of effects should be interpreted with caution. Also, variations in type of AAE (i.e., continuous, interval-based), duration, and specific post-AAE time-points TMS assessment present challenges in synthesizing the available data. To address this issue, we classified AAE interventions using ACSM intensity categories as a pragmatic solution to perform this meta-analysis, regardless of AAE type and duration. We also classified data into predefined post-AAE time windows to assess the duration of effects, which may have introduced confounds and biases into our results. Finally, few of the included studies reported levels of daily physical activity and cardiorespiratory fitness. With this information we could have characterized our observed effects of AAE on TMS-based measures of cortical excitability. Future studies should consider measuring physical activity and/or fitness of their participants.

5. Conclusion

Among the different neurophysiological measures assessed by TMS following AAE in young adults, decreased intracortical inhibition measured with $SICI_{2–5\ ms}$ was found to be the most consistent effect. This effect appeared to be driven by moderate- to high-intensity AAE. Corticospinal excitability was not increased overall, but an increase was observed after high intensity AAE following moderator analyses. Our results suggest potential mechanisms for the induction of a more susceptible neuroplastic environment following AAE. Understanding the underlying mechanisms by which AAE may impact M1 excitability, and the parameters of AAE (i.e., intensity, duration, type) that influence these changes, could be beneficial to inform AAE as an intervention to prime neuroplasticity and motor learning in sports and clinical contexts.

6. Future directions

Further research is required to elaborate associations between parameters of AAE (intensity, duration, and type), TMS parameters (e.g., corticospinal and/or intracortical excitability, stimulus intensities, ISIs, etc.), participant characteristics (e.g., physical activity levels, sex).

Although the current meta-regression analysis sheds light on the M1 excitability changes that occur following different AAE intensities, we have noted that there is a lack of data to make definitive conclusions. Specifically, there are very few studies that have used low-intensity AAE. Future studies should consider investigating the effects of multiple AAE intensities on M1 excitability measures to address this issue more comprehensively within one controlled study. Among the 23 studies included in our meta-analysis, one study reported using low-intensity AAE, however according to ACSM, the prescription used is equivalent to moderate intensity exercise. It is therefore important to note that prescribing AAE intensity is a crucial factor in the field of neuroscience and aerobic exercise.

Relatedly, AAE intensity should not be the only exercise parameter investigated and controlled for in future studies. The duration and type (e.g. continuous *vs.* interval) and mode (e.g. running and swimming) of exercise may play an important role in the impact of AAE on M1 excitability. Also, TMS parameters used to measure corticospinal and intracortical excitability varied widely across studies as discussed above. Future research in this field should consider adopting common TMS parameters (e.g., measuring SICI and TMS stimulus-response curves at standard stimulus intensities) to allow for easier comparison across studies and findings. Moreover, more work ought to be done taking into consideration participant characteristics, such as levels of physical activity, cardiorespiratory fitness, comparisons of sedentary and/or athletic populations. As there is evidence that physical activity levels impact the AAE-induced enhancement of M1 excitability (Lulic et al., 2017) and response to plasticity-inducing repetitive TMS protocols (Cirillo et al., 2009), this issue ought to be investigated further. Finally, more work is needed to understand the duration of AAE-induced changes to M1 excitability measures. Like the AAE and TMS parameters, post-AAE measurement timing and frequency varied dramatically across studies. There is a critical need to understand the duration of the effects of AAE on M1 excitability changes, which requires future research to utilize more common timepoints and frequency of post-AAE TMS assessment.

Declaration of interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105811.

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