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Review

Effects of Lactate on Corticospinal Excitability: A Scoping Review

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ABSTRACT

International Journal of Exercise Science 17(2): 1429-1443, 2024. Aerobic exercise has been shown to impact corticospinal excitability (CSE), however the mechanism(s) by which this occurs is unclear. Some evidence suggests an increase in blood lactate concentration resulting from exercise may be what is driving these changes in corticospinal excitability. The extent of literature examining this effect and whether it is consistent across the literature is unknown. As such, the objective of this scoping review was to summarize the existing literature examining the effect of lactate on corticospinal excitability and to determine any trend(s) in the effect. Embase, CINAHL, Medline, SPORTDiscus, and PsycInfo were systematically searched to retrieve original research reporting on blood lactate concentration and measures of corticospinal excitability associated with aerobic or high intensity interval exercise. Two reviewers independently determined study eligibility, and one reviewer extracted data from all eligible studies. The database search yielded 717 papers of which 9 were determined eligible. Multiple studies in which participants completed high intensity and/or exhaustive exercise showed a correlation between large increases in blood lactate concentration and increased corticospinal excitability, however several other studies noted no difference in corticospinal excitability following an increase in blood lactate concentration. This review showed that the existing body of literature is small and highly variable in both methods and results, therefore we can draw limited conclusions about the role of lactate, however based on the evidence available lactate does not appear to be the key player in the modulation of CSE. In addition, evidence from other literature supports moderate intensity aerobic exercise as a modulator of neuroplasticity, suggesting that there may be other key factors contributing to the changes in the brain following exercise.

KEY WORDS: Neurophysiology, metabolic by-products, transcranial magnetic stimulation, neurostimulation

INTRODUCTION

Aerobic exercise (AE) is known to mediate positive changes in the body and brain at the cellular, molecular, systemic, and functional levels. Specifically, both acute and chronic exercise have been shown to increase neuroplasticity (12, 25), the structural reorganization of neurons in the brain in response to repeated stimulation (1). Better understood not as a single event but rather

as a chain reaction of events that lead to improved cognitive function, neuroplasticity has been linked with improvements in learning. The finding that neuroplasticity and by extension, learning, can be effectively enhanced by both acute and chronic aerobic exercise is a promising one for clinical practitioners, coaches, and educators alike. However, despite the evidence that aerobic exercise can modulate these outcomes (13, 20, 28, 31), there is still much to be learned with respect to the exact mechanisms by which this takes place. A recently proposed mechanistic model of exercise-induced neuroplasticity suggests that change is first affected at the molecular and cellular level, and that these changes set the stage for the structural, functional, and behavioural changes that are often observed in both animal and human research (6). At the structural and functional level exercise increases corticospinal excitability (CSE) (6), an important prerequisite for learning to occur in the brain. This change in CSE is frequently measured through transcranial magnetic stimulation (TMS), a form of non-invasive brain stimulation which induces an electrical current to depolarize the neurons of the brain. Changes in CSE can be assessed through stimulation of the motor cortex, using electromyography (EMG) to measure a motor evoked potential (MEP) in the target muscle, the amplitude of which provides a measure of CSE. TMS can also be used to assess measures of cortical inhibition and facilitation through paired pulse stimulation, where a conditioning stimulus and test stimulus are delivered at set intervals. While a full overview of these TMS protocols is beyond the scope of this paper, a detailed review has been published by Ziemann and colleagues (33).

While there is evidence that even a single bout of AE can modulate CSE (6), the exact mechanisms underlying this effect remain unclear, and there is much to be explored regarding the specific dose-response relationship between AE and CSE and regarding participant-specific factors that influence the brain's response to AE. For example, Lulic and colleagues found that physically active individuals show an increased capacity for plasticity to occur when compared to sedentary individuals, but also found that exercise can be used to prime the brain for plasticity regardless of a participant's baseline physical activity level (10). However, no such relationship was found by MacDonald et al., showing that level of aerobic fitness did not predict the brain's response to a single bout of AE (11). A finding of note in the MacDonald study was the variability in individual participants' response to AE, with only approximately half showing an increase in CSE immediately after or 10 min after the cessation of exercise relative to pre-exercise levels. This variability in individual responses to AE appears to be prevalent in many studies, with substantial range in the measures used to assess the brain's response to AE. What drives this variability in response to AE is not yet understood.

One theory posits that the increased CSE following a bout of AE is related to the metabolites produced during exercise. A full analysis of the mechanisms thought to modulate CSE following exercise is beyond the scope of this review, however an excellent review has previously been completed by Taubert and colleagues. Briefly, exercise has been shown to increase peripheral levels of lactate, brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), dopamine, epinephrine, and norepinephrine (30). Several animal studies have elaborated upon the role of these metabolites in the brain, showing that lactate uptake in the brain increases the expression of BDNF (5) and that this uptake of lactate is critical for the formation of long term memory (29). Additionally, previous research

has demonstrated increased cerebral uptake of lactate in human subjects during exercise (19, 21), lending credibility to the theory that lactate is responsible for driving the increase in CSE seen following an acute bout of AE. Furthermore, another study showing increased CSE following a bout of AE found this same difference in individuals who received an intravenous lactate infusion but did not participate in the exercise session (3), reinforcing the hypothesis that increased CSE following exercise is driven by an increase in cerebral lactate concentration. Another study showed that an acute bout of high intensity exercise had greater effects on motor learning and consolidation when the exercise session was completed closer to skill acquisition, with more limited effects seen as the time between exercise and acquisition increased (31), suggesting that there exists an optimal concentration of exercise-induced metabolites to prime the brain for the acquisition of a motor skill. Despite these findings, several studies investigating the effects of exercise on motor learning have shown limited or no effects on performance or retention of a motor task despite an increase in CSE following either exercise alone (27) or a combination of exercise and skill training (24), or no difference in learning when exercise was completed at a moderate vs vigorous intensity (9). Although there is evidence that cerebral lactate increases proportional to arterial lactate during exercise (21), there remains much to be learned about the specific dose-response relationship between cerebral lactate and CSE as it relates to the learning and consolidation of a motor skill.

Given the current knowledge related to the effects of lactate on increased CSE and by association motor learning and consolidation, we performed a scoping review to evaluate the existing literature on the effects of AE on lactate as it relates to measures in the brain. The purpose of this review was to summarize the current research regarding lactate and measures in the brain, and to assess whether any trends exist in the literature that suggest an optimal intensity of exercise or concentration of cerebral lactate to create an optimal environment in the brain for plasticity to occur.

METHODS

The design and execution of this scoping review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines for scoping reviews (PRISMA-ScR) (32). To access and retrieve the available literature, we performed a comprehensive search of the following databases: Embase, CINAHL, Medline, SPORTdiscus, and PsycInfo. Keywords searched included: lactate, exercise, physical activity, and brain. Database specific subject headings were used where applicable to ensure that the keywords being searched would capture all potentially relevant articles. No limit was placed on year of publication; all databases were searched from their inception. The search strategy was developed with the help of an experienced research librarian. The full search strategy and PRISMA-ScR checklist are available in the supplementary material.

Following completion of the database search, all relevant articles were uploaded to Covidence and duplicate results were identified and removed, after which articles were screened twice; at title/abstract level and at full text level by two independent reviewers, with a third reviewer resolving any conflicts that occurred. Articles were included for review based on the following

criteria: 1) participants completed at least one session of either AE or high intensity interval training (HIIT); 2) a measure of the participants' blood lactate was obtained; and 3) at least one measure related to excitability of the brain through the use of transcranial magnetic stimulation (TMS) was obtained (e.g., stimulus-response curve, cortical silent period). Articles were excluded if the study did not meet all the above criteria. Studies looking at other exercise interventions such as resistance training or anaerobic exercise were not included as we were specifically interested in the effects of lactate in the brain following AE. Studies using HIIT were included because, although they involve intervals of high intensity exercise, they also often involve intervals of low to moderate intensity exercise, and as such may produce the effects that were of interest. Articles for which the full text was not available were excluded.

Following screening at full text, data was extracted into a custom form by one independent reviewer. The data extracted included study information (author, year, and country of publication), demographic information of participants (age range, sex, and health condition), information on the exercise intervention(s), information on participants' blood lactate levels (i.e., method of measurement, timepoints at which blood lactate was measured, and measurement values), and any information about measures of brain excitability included in the study (i.e., assessment of excitability that was performed, and the outcomes of these assessments). All articles underwent risk of bias assessment using the Critical Appraisal Skills Programme (CASP) checklist for cohort studies, and the references of all eligible articles were screened to identify any additional eligible studies.

RESULTS

The database search yielded a total of 717 studies from which 9 were determined to be eligible following full text screening. No additional references were identified following review of the reference lists of eligible articles. Figure 1 shows a summary of the screening process. Table 1 summarizes the participant demographics for each study as reported by the authors. Table 2 summarizes reported changes in both blood lactate level and measures in the brain following the exercise intervention.

The majority of studies enrolled young adults, with the notable exception of the two studies that recruited patients post-stroke and one study which recruited sedentary adults. The most commonly used exercise intervention was a maximal test to volitional exhaustion, used in four studies (3, 4, 17, 18). Two studies exclusively used a HIIT intervention (7, 8), while two other studies had their participants complete a combination of HIIT and moderate intensity exercise across multiple sessions (2, 16). Finally, one study assigned participants to one of either a HIIT group or a moderate intensity exercise group. Three studies involved multiple exercise sessions, one of which (15) assessed the effects of a six week program of either HIIT or moderate intensity exercise on mechanisms of central and peripheral fatigue. All studies measured blood lactate at baseline and at least once post-exercise, with the exception of one study (15) which exclusively used blood lactate measurements to determine lactate threshold and lactate turn point in participants completing a submaximal exercise test. Most studies measured blood lactate via a capillary sample, however three studies were an exception to this with two collecting venous

samples and the third collecting arterial samples. All nine of the studies included reported an increase in blood lactate concentration at the end of their exercise protocol, however only five of these nine studies noted a significant change in CSE following the increase in blood lactate concentration (2–4, 17). Five studies assessed CSE in an exercised muscle (2, 4, 7, 15, 16), with two of these noting significant increases in CSE following exercise (2, 4). The other four studies assessed CSE in a non-exercised muscle (3, 8, 17, 18), with three of these noting a significant increase in CSE (3, 8, 17) while the fourth demonstrated decreased voluntary activation of the nonexercised muscle in question (biceps brachii) (18).

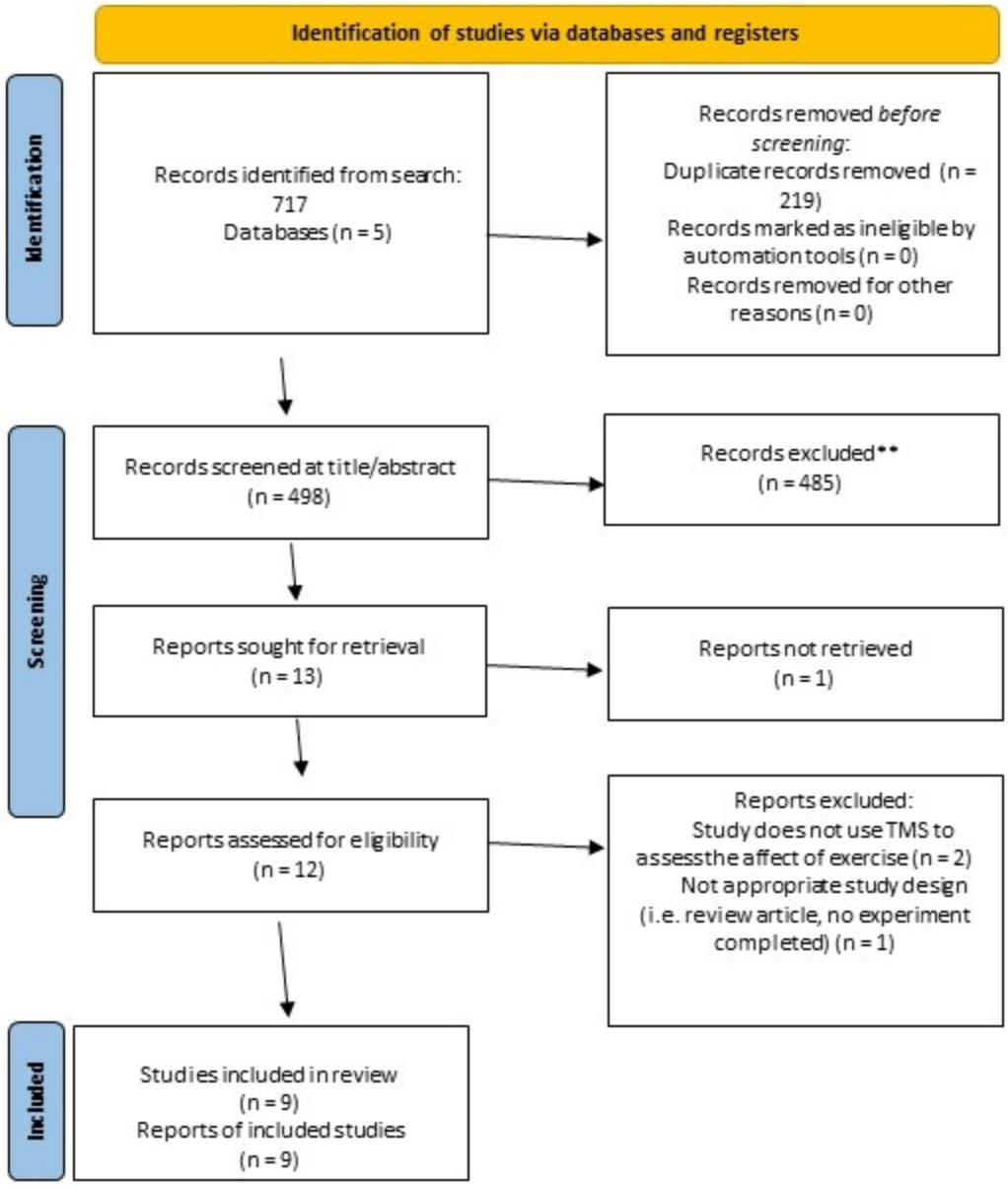

Figure 1. PRISMA diagram.

Table 1. Study demographics.

Reference	Participants (# Female)	Participant Ages*	Other Participant Characteristics	Exercise Intervention	TMS Procedures Used to Assess Brain Function	Assessment of CSE in Exercised vs. Nonexercised Muscle	Method of Lactate Measurement
Boyne et al. (2019)	16 (7)	37–72	Stroke patients with unilateral paresis	Combination of two different HIIT protocols (30s bursts at maximum tolerated treadmill speed or maximum tolerated seated stepper cadence, alternated with recovery periods) and moderate continuous exercise (treadmill speed continuously adjusted to achieve a mean moderate intensity of 45.5% HRR)	Single pulse TMS testing to measure the corticospinal activation threshold of the paretic quadriceps femoris (vastus lateralis) and the cortical silent period (CSP)	Exercised muscle (vastus lateralis)	Venous
Coco et al. (2010)	17 (0)	20.8 ± 2.21	University track and field athletes	Maximal test to volitional exhaustion (cycle ergometer)	Single pulse TMS at 120% of resting motor threshold (RMT) to measure activation of the first dorsal interosseus (FDI) muscle (5 MEPs averaged)	Nonexercised muscle (FDI)	Capillary

Coco et al. (2016)	28 (14)	27–51	Sedentary adults	Maximal test to volitional exhaustion (cycle ergometer)	Used a stimulus response curve to determine CSE of the primary motor cortex (using the FDI muscle) and supplementary motor area (using the tibialis anterior muscle)	Exercised muscle (tibialis anterior)	Venous
Goodall et al. (2015)	12 (0)	25 ± 6	Athletes training and competing in intermittent sprint sports	HIIT (repeated sprint protocol consisting of 12 x 30m sprints with 30s recovery)	Used TMS at 130% of RMT to assess CSE during maximal voluntary contraction of knee extensor muscles	Exercised muscle (biceps femoris and vastus lateralis)	Capillary
Li et al. (2019)	13 (2)	65.7 ± 7.2	Stroke patients with chronic unilateral stroke and contralateral hemiparesis	HIIT (5 minutes of high intensity treadmill walking where high intensity was defined as 75–85% of age predicted HRmax for participants not taking beta blockers, and an RPE of 13–15 on the Borg scale for participants on beta blockers)	CSE of the extensor carpi radialis (ECR) muscle was assessed by 10 MEPs from each hemisphere at 120% of RMT. Short interval cortical inhibition (SICI) was assessed for the same muscle using a conditioning stimulus of 90% RMT and a test stimulus of 130% RMT	Nonexercised muscle (ECR)	Capillary

O'Leary et al. (2017)	20 (4)	27 ± 6 (HIIT group) 27 ± 4 (CONT group)	Not engaged in any structured endurance training	HIIT group (6 repeats of 5 min cycling at an intensity of 50% of the difference between VO2max and lactate threshold) and CONT/moderate intensity group (same volume of work completed in the HIIT protocol but at 90% of lactate threshold)	Assessed CSE of the vastus lateralis muscle through TMS at 130% of RMT	Exercised muscle (vastus lateralis)	Capillary
O'Leary et al. (2016)	16 (0)	25 ± 5	Recreationally active individuals	Combination of HIIT (exercise at an intensity of 50% of the difference between VO2max and lactate threshold) and moderate continuous exercise (exercise at 90% of lactate threshold)	Assessed CSE of the vastus lateralis muscle through single pulse TMS at 130% of RMT; used single pulse TMS at 120% of RMT to assess MEP amplitude and CSP; used paired pulse TMS to assess SICI and intracortical facilitation (ICF) with a conditioning stimulus at 90% RMT and test stimulus at 120% RMT	Exercised muscle (vastus lateralis)	Capillary
Perciavalle et al. (2010)	41 (20)	21 ± 1.62 (females) 21.7 ± 1.84 (males)	Middle distance university track and field athletes	Maximal test to volitional exhaustion (cycle ergometer)	Used TMS at 120% RMT to assess cortical excitability (average of 5 MEPs)	Nonexercised muscle (FDI)	Capillary

Rasmussen et al. (2010)	15 (0)	18–34	Not reported	Combination of submaximal workload (95% of the workload the subject could sustain for 20 min at an FiO2 of 0.10) and maximal test to volitional exhaustion	Used twitch interpolation with TMS at 70–90% of maximal stimulator intensity to assess voluntary activation of the biceps brachii	Nonexercised muscle (biceps brachii)	Arterial

Table 2. Changes* in blood lactate and brain measures following exercise.

Reference	Blood Lactate	Brain Measures
Boyne et al. (2019)	High intensity treadmill and high intensity stepping exercise elicited significantly higher changes in blood lactate than moderate intensity treadmill exercise	Significantly greater acute increase in CSE following high intensity treadmill exercise when compared to moderate intensity treadmill exercise
Coco et al. (2010)	Significant increase in blood lactate following exhaustive exercise	Significant change in CSE as shown by a decrease in resting motor threshold following exhaustive exercise
Coco et al. (2016)	Significant increase in blood lactate following exhaustive exercise	Significant increase in CSE of primary motor cortex and decrease in CSE of SMA following exhaustive exercise
Goodall et al. (2015)	Increase in blood lactate observed from third repetition of HIIT protocol, blood lactate continued to increase throughout the rest of the exercise protocol	Decrease in maximal voluntary contraction following a HIIT protocol (repeated sprint exercise) but no change in MEP amplitude or CSP
Li et al. (2019)	Blood lactate levels increased significantly post exercise intervention (HIIT protocol)	Increase in excitability (defined as an increase in peak-to-peak resting MEP amplitudes) in the lesioned hemisphere of the brain following exercise
O'Leary et al. (2017)	Blood lactate values were only used to determine lactate threshold and lactate turn point for further exercise sessions	HIIT training was shown to attenuate central fatigue (assessed via TMS of the vastus lateralis and biceps femoris) when compared to moderate intensity continuous training, however neither HIIT nor moderate intensity exercise had any significant impact on MEP amplitude
O'Leary et al. (2016)	Lactate increased following suprathreshold (severe intensity) exercise but did not increase following moderate intensity exercise	Saw an increase in SICI and shortening of the CSP following suprathreshold (severe intensity) exercise and a decrease in ICF following moderate intensity exercise; MEPs were unchanged (showing that this exercise did not significantly alter CSE)
Perciavalle et al. (2010)	Saw a significant increase in blood lactate following exhaustive exercise	Significant decrease in resting motor threshold following exhaustive exercise
Rasmussen et al. (2010)	Increase in blood lactate following exercise in hypoxic conditions and maximal exercise, no change in blood lactate following low intensity exercise	Saw a decrease in voluntary activation of the elbow flexors following maximal exercise

*Where specified, "significant" indicates a statistically significant difference ($p < 0.05$).

DISCUSSION

The existing body of literature, although small, provides some evidence that lactate may be responsible for modulating CSE following exercise. Four studies examining the effects of lactate on CSE saw significant changes in CSE - defined as either increased excitability or a decreased resting motor threshold in the primary motor cortex (M1) - following a bout of either HIIT or maximal exercise to volitional exhaustion. Additionally, one of these studies noted an associative decrease in excitability of the supplementary motor area (4), suggesting that an increase in M1 excitability following an exercise-induced increase in blood lactate does not necessarily extend to other areas of the brain, however how excitability of this brain region was assessed using TMS was not clear. It is important to note that of the three other studies that saw an increase in CSE following exercise-induced lactate accumulation, one study also observed this same increase in CSE in participants that underwent a lactate infusion at rest, further supporting the hypothesis that lactate is a driving factor in the changes in the brain that occur following a bout of exercise (3). Another study observing significant decreases in CSE following a single bout of exhaustive exercise also noted a significant difference between the motor threshold of males and females five minutes post-exercise, suggesting that lactate-induced mediation of CSE has a greater effect in females (17). Perhaps the most interesting observation comes from one of two studies investigating exercise-mediated effects on CSE in a cohort of stroke patients, showing an increase in CSE in the lesioned hemisphere of the brain following a treadmill HIIT protocol resulting in a significant increase in blood lactate (8). Another study of a stroke cohort also saw a significant increase in CSE following a HIIT treadmill protocol when compared to a moderate intensity treadmill protocol, however the investigators suggest that this increase in CSE in the injured hemisphere is actually driven by an increase in circulating BDNF (2). While this increase in BDNF was associated with an increase in lactate, suggesting that an increase in circulating BDNF is driven by lactate accumulation, the analysis performed by these authors suggests that blood lactate had a negative effect on CSE that was mediated by the positive effects of exercise intensity. Furthermore, two additional studies saw no changes in CSE despite significant blood lactate accumulation following a bout of HIIT exercise (7, 16).

In addition to its potential to modulate CSE, there is evidence that exercise intensity plays an important role in modulating central fatigue, a reduction in the ability to activate the muscle owing to inhibition of cortical neurons. More importantly, central fatigue may be modulated independently of CSE, as shown by Goodall et al. (7), who saw an increase in central fatigue following a repeated sprint HIIT protocol, but no change in CSE post-exercise. The role of lactate, however, is unclear, with Coco et al. (3) suggesting that increased lactate concentration does not influence central fatigue, while Goodall et al. (7) measured increased central fatigue following a HIIT protocol that also resulted in increased blood lactate concentration. Interestingly, one study showed that a HIIT program can attenuate central fatigue significantly compared to a moderate intensity training program, however the investigators did not measure blood lactate at any point during the training program (15). Of particular interest is the finding that exercise decreased voluntary activation of a non-exercised muscle (18), suggesting a global effect of central fatigue.

All studies included in this review studied the effects of exercise on the brain using either a maximal exercise test to volitional exhaustion, or a study with a HIIT component (by randomizing participants to complete HIIT vs low-moderate exercise, or by having all participants complete both HIIT and low-moderate exercise sessions). Consequently, all studies saw an increase in blood lactate concentration following exercise, as it is to be expected that participants completing HIIT or maximal exercise to exhaustion would be exercising above their lactate threshold. It is also therefore unsurprising that the studies measuring blood lactate level following either moderate or low intensity exercise did not see the same increase that was noted after HIIT or maximal exercise (2, 16, 18). Interestingly, some of the literature surrounding exercise-driven neuroplasticity suggests that exercise performed at a moderate intensity may be optimal for modulating CSE and plasticity in the brain (11, 22–24, 26), demonstrating that CSE does not necessarily increase linearly with blood lactate. This could suggest that an accumulation of lactate is not, in fact, the driving factor behind increased CSE. It is possible that there exists an optimal concentration of blood lactate for modulating CSE through exercise, however further research is needed to confirm this. It is also possible that this exercise-driven change in CSE is related to an increase in BDNF rather than lactate. BDNF has been shown to increase concurrently with lactate, and research suggests that the optimal intensity of exercise to elicit the greatest possible BDNF response is at or around the onset of blood lactate accumulation (2). However, much of the current literature focuses primarily on the role of lactate due to the ease of sample collection and analysis, and more research is needed on the specific role of BDNF as it relates to changes in CSE.

The goal of this review was to assess and analyze the existing literature on exercise-driven effects of lactate in the brain. It should be noted that the available body of literature is small and of the studies meeting our eligibility criteria, several did not report directly on the effects of lactate on the brain despite measuring both blood lactate and at least one measure of brain excitability through TMS. While there is evidence that exercise can mediate changes in intracortical measures such as short-interval cortical inhibition (SICI) and intracortical facilitation (ICF) even in the absence of increased corticospinal excitability (14, 16), intracortical measures remain understudied in the literature (only reported in two of nine studies in this review). Furthermore, of the research available many studies featured small sample sizes (six studies with $n < 20$), and four studies exclusively recruited male participants, limiting generalizability of their results. It is also difficult to draw comparisons between these studies because, although many used HIIT or exhaustive exercise protocols, there was variety in the types of protocols used (e.g., treadmill or track sprints vs cycle ergometer) and in the means of determining exercise intensity, with some studies using heart rate reserve, others using VO_{2max} or lactate threshold, and still others using age predicted maximal heart rate or rating of perceived exertion. The lack of a consistent exercise protocol across studies limits the generalizability of results and makes it difficult to draw conclusions about any potential effect of exercise type on lactate-mediated changes in the brain. Additionally, while about half of the studies had participants complete exhaustive exercise and/or had participants complete the exercise intervention at a predetermined percentage of their lactate threshold, several studies used other methods to determine intensity. Use of an approximation method such as maximum tolerated speed or percentage of maximal heart rate to determine exercise intensity can result in some individuals exercising above their

lactate threshold with others exercising below it, potentially producing highly variable results as not all participants are equally aerobically trained and therefore not all responding to the exercise intervention in the same way. Finally, since our goal was primarily to assess the role of lactate, we also did not extend our search to capture other metabolic byproducts of exercise with the potential to modulate CSE, such as BDNF, which is something that could be considered for a future review.

The role of lactate in the modulation of CSE following exercise remains unclear. While there is evidence in the literature to support a lactate-driven increase in CSE, there are also studies showing no effect on CSE following an increase in lactate. Furthermore, the current literature supports moderate intensity exercise as a modulator of neuroplasticity, suggesting that while lactate may have a role in modulating CSE, there are likely other factors contributing to the changes in the brain following a bout of exercise. Further research is necessary to determine the level to which metabolic byproducts of exercise, among them lactate, contribute to the modulation of CSE. Future work should consider having the same individuals exercise at various percentages of their lactate threshold to determine whether there is an effect on exercise intensity on CSE as it relates to blood lactate concentration. Additionally, future work comparing low, moderate, and high intensities of exercise could consider including BDNF levels as a covariate in the analysis.

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