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Review

Transcranial magnetic stimulation probes the excitability of the primary motor cortex: A framework to account for the facilitating effects of acute whole-body exercise on motor processes

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Abstract

The effects of exercise on decision-making performance have been studied using a wide variety of cognitive tasks and exercise interventions. Although the current literature supports a beneficial influence of acute exercise on cognitive performance, the mechanisms underlying this phenomenon have not yet been elucidated. We review studies that used single-pulse transcranial magnetic stimulation (TMS) to probe the excitability of motor structures during whole-body exercise and present a framework to account for the facilitating effects of acute exercise on motor processes. Recent results suggest that, even in the absence of fatigue, the increase in corticospinal excitability classically reported during submaximal and exhausting exercises may be accompanied by a reduction in intracortical inhibition. We propose that reduced intracortical inhibition elicits an adaptive central mechanism that counteracts the progressive reduction in muscle responsiveness caused by peripheral fatigue. Such a reduction would render the motor cortex more sensitive to upstream influences, thus causing increased corticospinal excitability. Furthermore, reduction of intracortical inhibition may account for the more efficient descending drive and for the improvement of reaction time performance during exercise. The adaptive modulation in intracortical inhibition could be implemented through a general increase in reticular activation that would further account for enhanced sensory sensitivity.

Keywords: Corticospinal excitability; Exercise-cognitive function interaction; Intracortical inhibition; Transcranial magnetic stimulation

1. Introduction

The effects of exercise on decision-making performance have been studied using a wide variety of cognitive tasks in conjunction with exercise interventions inducing a range of physiological changes in core temperature, blood glucose concentration, and muscle/cerebral oxygenation. The current literature supports a beneficial influence of acute exercise on cognitive performance.[1–3] However, the mechanisms underlying this phenomenon have not yet been elucidated. In this paper, we review studies that used single-pulse transcranial magnetic stimulation (TMS) to probe the excitability of motor structures during whole-body exercise. We present a framework that accounts for the facilitating effects of acute exercise on motor processes during cognitive tasks.

2. Acute bout of exercise and cognitive function

Cognitive facilitation is more consistently observed during moderate acute exercise and usually disappears at higher exercise intensities. Several authors claim that above a certain

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level of physical stress, exercise disrupts cognitive functioning,[4,5] suggesting that intensity and duration are determining factors in the acute exercise−cognition relationship.[6] According to the transient hypofrontality theory,[7] strenuous exercise causes extensive activation of motor and sensory systems that contribute to the recruitment of motor units, sensory input integration, and regulation of the autonomic systems. Due to limited cognitive resources available, this huge solicitation induces competition for resources which alters cerebral oxygenation and renders the frontal lobes hypoactive.

However, deficits in prefrontal-dependent cognitive tasks are not always observed. McMorris et al.[8] failed to observe a deterioration in cognitive control, a crucial element in decision-making, despite very high exercise-induced physiological stress (i.e., 80% of maximal aerobic power (MAP)) while Davranche and Pichon[9] reported enhanced sensory sensitivity after an incremental exercise test to task failure. The effect of acute exercise on the cognitive tasks used in these studies (e.g., reaction time (RT), visual discrimination) may result from the activation of the reticular-activating system.[4] The increased arousal, that is induced by enhanced activity of the noradrenergic and dopaminergic systems, permits sustained physical exercise by massively recruiting motor units and activating the autonomic and endocrine systems. By improving early sensory sensibility and motor process efficiency, the reticular-activating system is probably also responsible for shortening motor times and enhancing sensory sensitivity.

3. A chronometric and electromyographic approach to assess the effect of exercise on RT

Mental chronometry is the most widespread method used to assess the effects of exercise on cognitive processes. The paradigm of mental chronometry is based on the notion that cognitive processes can be assessed by measuring the time required for information processing. Indeed, a number of inferences can be made using the measure of RT. RT corresponds to the time that elapses between the onset of a stimulus and the occurrence of an overt response. The mental chronometry method consists of measuring RT in different conditions and, when all other factors are equal, RT differences are used to make inferences regarding the influence of the different conditions on cognitive processing. Electrophysiological techniques (e.g., single neuron activity, electrical and magnetic stimulation, electroencephalography, magnetoencephalography) can also be used in conjunction with RT measures to make inferences based on observations of physiological changes. The general principle is to combine electrophysiological and mental chronometry techniques in order to record indices related to the nature and organization of the cognitive processes. For example, the locus of the effect of an experimental factor can be addressed using fractionated RT with respect to the changes in electrophysiological activity.[10] The electromyographic (EMG) activity of the response agonists allows such a fractioning. The time interval between the onset of the response signal and the onset of EMG activity is termed “premotor time”, while the time interval between the onset of EMG activity and the onset of the required motor response is termed “motor time”.

The combination of electrophysiological and mental chronometry techniques has been used to study the effects of exercise on cognitive function. Two RT experiments, one using a choice RT test and the other one using a simple RT task, were carried out and the EMG activity of the response agonist muscle involved in the task was recorded during exercise.[11] With this paradigm, Davranche et al.[12,13] showed that RT facilitation is mostly due to a shortening in the duration of the motor time (i.e., motor processes involved in response execution). Based on indirect arguments relative to the steepness of the rectified EMG burst during exercise, the authors suggested that the corticospinal command provides a more efficient descending drive while exercising than at rest. This improvement could be due to changes in the excitability of corticofugal neurons and/or cortical neurons projecting directly or oligosynaptically onto these cells. One way to directly assess changes in corticospinal tract excitability induced by exercise is to use single-pulse TMS to assess the excitability of motor cortical structures during whole-body exercise.

4. TMS of the motor cortex reveals neural activation and suppression

TMS is a non-invasive, safe and relatively painless technique to investigate the motor cortex by producing a magnetic field that elicits an electrical current in the brain. The delivery of single- or paired-pulse TMS is often used to characterize alterations in central motor pathways. When the muscles are tonically contracted, TMS of the cortical zones that control these muscles evokes two events in the ongoing EMG. First, due to the direct and transynaptic recruitment of corticospinal neurons, TMS causes a synchronous discharge of the motoneuronal pool reflected by the motor-evoked potential (MEP).[14] The MEP is followed by a silent period (SP) in the ongoing tonic EMG activity. While the initial part of the SP is a direct consequence of the MEP (refractory period of neurons involved in the MEP, pause in spindle firing, or Renshaw inhibition), the latter part results from the recruitment of inhibitory gamma-aminobutyric acid (GABA)-ergic interneurons within the motor cortex.[14−18] When the stimulus intensity is constant, variations in MEP amplitude reflect changes in the excitability of the corticospinal tract while changes in SP duration reflect intracortical inhibitory influences projecting onto this pathway.

Using single-pulse TMS of the primary motor cortex to stimulate the agonist muscle involved in an RT task, Davranche et al.[19] and Tandonnet et al.[20] investigated the neural mechanisms of temporal preparation. Through SP duration and MEP amplitude measures, TMS was used to investigate corticospinal tract excitability and intracortical inhibitory influences before (during the foreperiod) and during the RT interval. The TMS intensity was set at 105% the minimum

intensity to produce a MEP with a peak-to-peak amplitude of approximately 100 μV during isometric voluntary contractions at 10−20 N (mean intensity = 38% ± 4% of maximum stimulator output). The SP duration progressively decreased during the foreperiod suggesting that temporal preparation is accompanied by a removal of intracortical inhibition. Moreover, MEP area decreased over the course of the foreperiod, indicating that temporal preparation involves an overall reduction in the excitability of the corticospinal pathway. Davranche et al.[19] proposed that this reduction in corticospinal excitability secures the development of preparatory cortical activation, preventing erroneous premature responses. Using the same TMS methodology, Tandonnet et al.[20] reported a reduction in SP duration during the RT interval, providing evidence that temporal preparation involves an early cortical disinhibition. The authors proposed that this cortical disinhibition increases the efficiency of the motor system and leads to faster response implementation.

Single-pulse TMS of the primary motor cortex thus provides a unique opportunity to study changes in the excitability of the corticospinal pathway during cognitive processing. This technique could enrich our understanding of the exercise-cognition interaction by providing insights relative to neural modulation during exercise. In particular, a more efficient descending drive during exercise[12,13] may be associated with an increase in MEP amplitude. Furthermore, if exercise enhances the excitability of the primary motor cortex by reducing intracortical inhibition, the duration of the SP elicited in the same muscles should be shortened.

5. TMS of the motor cortex and neuromuscular fatigue

Single-pulse TMS of the primary motor cortex is also used in the field of exercise physiology to better understand the contribution of central processes to neuromuscular fatigue. The design of the studies has generally consisted of an isometric fatiguing exercise of lower- or upper-limb muscles. However, research protocols vary greatly by exercise modality (i.e., single-joint *vs.* whole-body exercise), exercise intensity (i.e., maximal *vs.* submaximal), exercise duration (10 × 6-s sprints to >13 h), exercise protocol (i.e., intermittent *vs.* continuous) and TMS intensity. The manner in which exercise influences neuromuscular function appears related to these variables. Task-dependent differences in cortical and spinal responses to fatigue are likely linked to differences in both systemic and local (i.e., muscular) changes. In comparison to single-joint exercises, whole-body exercises have higher cardiorespiratory and metabolic requirements which lead to systemic responses such as changes in temperature regulation, glucose availability, catecholamine concentration, and cerebral oxygenation that could affect the excitability of motor structures.[21] Considering that measures of the effects of exercise on cognitive function are classically obtained during acute bouts of running or cycling (whole-body exercises), muscle groups working in isolation have little interest from a systemic point of view. Thus, in the framework of this discussion, we focus primarily on studies that investigated acute whole-body exercise.

Only a limited number of studies have used TMS to investigate neural excitability after acute whole-body exercise. Due to the difficulties in performing TMS during whole-body exercise, most investigations have compared changes pre- and post-exercise. One limitation of these studies is that there is a delay between the end of the exercise bout and the assessment of post-exercise measures, largely due to the time required to transfer subjects from an ergometer for whole-body dynamic exercise to another ergometer to perform isometric contractions and TMS, the current standard in neuromuscular evaluation. In fatiguing upper-body isometric contraction protocols, MEPs and SPs have been shown to recover within ∼30 s of exercise cessation.[22] Similarly, central activation and SPs have been shown to recover within 2 min post-exercise in an isometric lower limb protocol.[23] However, it has been suggested that exercise duration may also influence the ability to detect measureable post-exercise changes in TMS parameters and single-joint protocols are only of limited duration. For example, in whole-body dynamic exercise, MEP, SP, and central activation changes after a 110-km ultra-trail running race were present ∼1 h post-exercise.[24] Sidhu and colleagues[25,26] have recently incorporated TMS evaluation of MEPs and intracortical inhibition during cycling protocols to overcome the limitation of delayed post-exercise measurement, and thus permit better understanding of the effects of exercise on corticospinal excitability and inhibition.

Initial investigations into MEP changes with exercise compared changes in absolute MEP size at rest.[27] However, comparisons of absolute MEP size do not account for activity-dependent changes in peripheral signal conduction (i.e., at the muscle level and independent of corticospinal mechanisms). Therefore, since MEPs are measured by surface EMG, it is essential to systematically normalize MEP amplitude/area to the concomitant M-wave elicited by supramaximal peripheral nerve stimulation (M_{max}) in the same muscle state. While absolute MEP amplitude can be modified due to alterations in signal conduction at any level from the motor cortex to within the muscle, changes in MEP/M_{max} specifically indicate modifications at the corticospinal level.

Another consideration with TMS investigations is the TMS intensity. Different methods of determining TMS intensity and their subsequent application (i.e., percentage of determined TMS intensity) result in a large difference in TMS intensities across studies.[28] While most exercise studies have evaluated MEP size and SP duration at intensities expected to elicit maximal or near-maximal MEP or evoked mechanical responses, the ability of TMS at low intensities to influence the most direct motor cortical projections to the spinal motoneurons has also been employed to investigate intracortical inhibition during muscular activity.[29] As the TMS intensity is reduced below active motor threshold (the intensity to elicit MEPs half the time during voluntary contraction), the frequency and amplitude of MEPs diminishes until there are no longer MEPs, only just facilitation of the EMG signal (i.e., marginally increased EMG activity in the timeframe of

interest). Eventually, as TMS intensity is decreased further, the minimal cortical output to descending motoneurons causes a suppression of voluntary EMG activity.[29–31] Changes in the amount of EMG suppression during exercise are believed to be indicative of resulting changes in intracortical inhibition.

5.1. Effect of whole-body exercise on MEPs

Most studies have failed to observe any change in MEP/M_{max} in response to whole-body exercise. For example, Goodall et al.[32] did not observe changes in MEP/M_{max} area after constant load cycling at 80% MAP to task failure. Similarly, no changes in MEP/M_{max} were observed 2–3 min after eight 5-min bouts of cycling at 80% MAP separated by 1 min[33] and 10 min after ~1.5 h cycling.[34] Two other studies specifically examining cycling sprint performance reported contradictory results. Girard et al.[35] observed unchanged MEP/M_{max} amplitude after a series of fifteen 6-s sprints. Conversely, after 30-s all-out sprints, Fernandez-del-Olmo et al.[36] reported increased MEP/M_{max} area.

Increased corticospinal excitability has also been observed during two recent submaximal cycling studies. Two to 3 min after 40 min of cycling at 65% MAP and also subsequent incremental exercise until task failure, Temesi et al.[37] observed increased MEP/M_{max} amplitude. Similarly, after three series of 80 min of cycling at 45% MAP, Jubeau et al.[38] reported increased MEP/M_{max}. After a recent 110-km trail running race, increased MEP amplitude was reported despite ~1 h delay to post-race assessment.[24] The increase in MEP amplitude observed after prolonged submaximal exercise,[37,38] incremental exercise to task failure,[37] very short maximal exercise[36] or an ultra-endurance exercise bout[24] may be interpreted as a compensatory mechanism to generate the required motor output and overcome the reduced peripheral force production capacity.

5.2. Effect of whole-body exercise on intracortical inhibition

Although most published studies failed to observe changes in SP,[32–36,38,39] two recent reports suggest altered intracortical inhibition during whole-body exercise.[26,37] These two studies are detailed below since they support the possibility of decreased intracortical inhibition during moderate duration exercise where cognitive facilitation has been observed.

Using sub-threshold TMS intensities (mean = 18.5% ± 0.8% of maximum stimulator output), Sidhu et al.[26] investigated changes in the responsiveness of the intracortical inhibitory interneurons during sustained cycling exercise. TMS was delivered during a sustained 30-min cycling bout at 75% MAP and during nonfatiguing control cycling bouts at 75% and 37.5% MAP (consisting of repeated 1-min cycling bouts). At the end of the sustained cycling bout, subjects were required to cycle for an additional 5 min at 37.5% MAP and TMS was delivered at the same intensity as during the 30-min cycling. In some subjects not showing initial EMG suppression, suppression of the ongoing EMG developed during the 30-min cycling bout and became evident in the last 5 min. The increase in TMS-evoked EMG suppression was interpreted as an increase in the excitability of the intracortical inhibitory interneurons. However, conclusions made from EMG suppression are equivocal due to the large number of subjects where EMG suppression without prior facilitation was not observed (during cycling, only 8 of 16 subjects for vastus lateralis and tibialis anterior and 9 of 16 subjects for biceps femoris met inclusion criteria). Furthermore, several subjects demonstrating EMG suppression before the cycling task developed EMG facilitation during the cycling task, possibly suggesting decreased intracortical inhibition.

Temesi et al.[37] was the first, and only, study to report decreased intracortical inhibition with whole-body exercise. Using a TMS intensity designed to elicit maximal MEP amplitudes (mean intensity = 63% ± 10% of maximum stimulator output), changes in the responsiveness of intracortical excitatory interneurons with sustained cycling exercise were evaluated. TMS was delivered before and after 40-min submaximal cycling and a subsequent incremental cycling test to task failure. After 40-min cycling at 65% MAP, neuromuscular testing showed that the intensity and duration of the physical exercise was not sufficient to induce central fatigue. Interestingly, decreased SP duration (indicative of decreased inhibition within the motor cortex) and increased MEP amplitude (indicative of increased excitability at the level of the corticospinal pathway) were observed. Following the subsequent incremental exercise to task failure, there was a reduced capacity to maximally drive the muscles (i.e., decreased maximal voluntary activation level), demonstrating the development of central fatigue. Concomitant to this decline in muscle recruitment, a decrease in SP duration and an increase in MEP amplitude were observed. These findings may be interpreted as a reduction of intracortical inhibition. As intracortical inhibitory interneurons project onto excitatory neurons whose activation generates the MEP, it is possible that the reduction in intracortical inhibition contributed to the increase in corticospinal excitability. This suggests that the cortical inhibition exerted on the corticospinal tract may be partly removed when exercising. We believe that, even in the absence of fatigue, the CNS can influence the corticospinal excitability level during prolonged exercise via the modulation of intracortical inhibition to maintain the motor cortex highly activated.

6. Exercise enhances the excitability of the primary motor cortex over time (by reducing cortical inhibition)

The use of single-pulse TMS of the primary motor cortex, in the context of neuromuscular fatigue, with whole-body exercise provides insight into neural modulation during exercise that may account for the facilitating effects of acute exercise on motor processes during cognitive tasks. This review highlights an increase in corticospinal excitability after steady-state submaximal exercise, incremental exercise to task failure, and very short maximal exercise.[36–38] A decrease in SP duration has been observed both after a cycling test to task failure and after a steady-state submaximal cycling bout despite the absence of signs of central fatigue.[37] This new finding reveals that a reduction in intracortical inhibition may

accompany the increase in corticospinal excitability often observed with exercise.

It is reasonable to suggest that the increase in corticospinal excitability indicated by an increase in MEP amplitude may actually result from changes in excitability within the motor cortex. Reduced SP while exercising, would make the motor cortex more sensitive to upstream influences and increase corticospinal excitability. We believe that this mechanism underlies a central adaptation that counteracts the progressive reduction in muscle responsiveness caused by peripheral fatigue. Similarly, the reduction in intracortical inhibition may account for the more efficient descending drive and for the reduction of RT performance during exercise.[12,13] The adaptive changes in intracortical inhibition could occur through a general increase in reticular activation[4] that would further account for enhanced sensory sensitivity.[9,40]

To date, single pulse TMS studies have been conducted while performing RT tasks[19,20] or after/during acute whole-body exercise; however, no studies have simultaneously assessed RT task performance and TMS responses during whole-body exercise. For the moment, it is thus impossible to provide direct evidence of a causal link between the excitability of the corticospinal pathway, cognitive performance changes, and physical exercise (including the effect of exercise intensity and duration). Future studies using single-pulse TMS of the primary motor cortex should be conducted within a paradigm of mental chronometry while exercising to test this relationship. During exercise, we also anticipate that the pattern of TMS responses (MEP amplitude/area and SP duration changes) will differ depending on the characteristics of the muscle investigated. Indeed, it would be interesting to assess whether similar changes could be observed when TMS targets cortical zones controlling the agonist muscle involved in a cognitive task or the muscles involved in locomotion.

7. Conclusion

In the current paper, we reviewed studies that used single-pulse TMS of the primary motor cortex with whole-body exercise and presented a framework that may account for the facilitating effects of acute exercise on motor processes during cognitive tasks. This review suggests that a reduction in intracortical inhibition may accompany the increase in corticospinal excitability classically reported during submaximal and exhausting exercises, and provides an alternative viewport to explain the underlying mechanisms between acute exercise and cognition.

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