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Locomotor activities as a way of inducing neuroplasticity: insights and perspectives on conventional and eccentric exercise approaches

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Abstract

Conventional locomotor exercise, such as cycling or walking, induces motor learning-like neuroplastic changes (i.e., decreased cortical inhibition and/or increased facilitation, assessed in a muscle using transcranial magnetic stimulation). These effects seem to be a consequence of humoral processes notably resulting from hemodynamic solicitation. Unfortunately, pathological populations may not be capable of exercising at sufficient intensities to trigger these beneficial neuroplastic modulations and an alternative method is needed. As it can be inferred from non-invasive brain and peripheral stimulation studies, a high neural activity can directly result in neuroplastic changes. Similarly, eccentric exercise (i.e., active lengthening of the muscle), during which individuals develop the same force or power as conventional exercise at lower cardiorespiratory intensities, requires a high brain neural activity. As single-joint eccentric exercise was decreased cortical inhibition and increased cortical facilitation, locomotor eccentric exercise may be even more potent by pooling neural and, maybe, hemodynamic neuroplastic processes. Further studies are required to understand the influence of locomotor exercise characteristics (e.g., intensity, duration) on exercise-induced neuroplasticity.

Keywords

Transcranial magnetic stimulation; Corticospinal excitability; Cortical inhibition; Cortical facilitation; Eccentric cycling

Highlights:

- Conventional locomotor task induces neuroplastic changes beneficial to patients.
- These effects can come from either hemodynamic of neural mechanisms.

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- Locomotor eccentric exercise may pool both processes at low respiratory intensity.
- Studies are needed on the effects of exercise features on induced neuroplasticity.

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Introduction

During exercise, the primary motor cortex sends electrical impulses to trigger voluntary muscle contractions. The signal goes through nerves along the spinal cord (also termed corticospinal -CS- pathway), before reaching the alpha motoneuron, and then the muscle fibers it innervates. CS excitability, tested by transcranial magnetic stimulation (TMS) applied over the primary motor cortex, refers to "the efficacy of the corticospinal pathway to relay neural signals from higher brain areas to the muscle" [1]. For stimulation intensity higher than the motor threshold, single pulse TMS evokes an electrophysiological response in the targeted muscle, termed motor evoked potential (MEP). MEP amplitude indicates the level of excitation of cortical neurons mono- or trans-synaptically connected to spinal motoneurons [2]. During voluntary contraction, the MEP is followed by the absence of muscle activity -silent period-, that mirrors the duration of inhibitions located at the cortical [3] and spinal levels [4, 5]. Paired-pulse TMS protocols also evidenced that the recruitment of cortical neurons is mediated by inhibitory and facilitatory processes interacting at the cortical level (see [6] for a review). Any change in CS excitability, cortical inhibition or facilitation would reflect the occurrence of neuroplastic processes [7], by which the central nervous system modifies its structure and functioning to encode new experience [8]. Particularly, changes in the balance between cortical inhibition and facilitation could be determinant for ontogenetic development [9] or learning a simple motor task [10]. Moreover, individuals with neurodegenerative diseases (for a review see [11] or recovering from stroke (e.g. [12, 13]) also show changes in this balance, which could impair motor or executive functions. In this context, neurorehabilitation protocols using non-invasive brain stimulation techniques such as repetitive TMS or paired-associative stimulation have been developed in order to counteract deleterious neuroplasticity [14]. Despite a growing interest for these techniques in the past two decades, limitations such as their expensiveness and precautions of use in certain individuals (e.g., those

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with epilepsy) hinder their use in a wide population. Physical activity has thus been considered as a promising alternative strategy to modulate neuroplasticity in rehabilitation protocols.

This article provides a review of 1) the impact of conventional locomotor exercise on neuroplasticity assessed in non-exercised or exercised muscles; 2) likely underlying neuroplastic processes triggered by the hemodynamic flow; 3) insights from non-invasive brain and peripheral stimulation studies on the nervous mechanisms resulting in neuroplastic changes ; 4) eccentric exercise and more specifically locomotor tasks within this category as a way to merge neural and hemodynamic factors associated with neuroplastic changes.

1. Physical exercise induces neuroplasticity

Physical exercise has consistently been reported as an efficient stimulus promoting neuroplasticity. Brain neural adaptations resulting from aerobic exercise appear to have similarities with those associated with the learning of a simple motor action, namely increased number of synapses in neural networks and reduced cortical inhibition [10]- the latter adaptation would be a prerequisite for neuroplasticity [15]. These mechanisms could have accounted for improved motor skills retention in patients with chronic stroke [16] or Parkinson disease [17], when motor practice was implemented in addition to aerobic exercise. While physical exercise appears as a potent neurorehabilitation tool, it is challenging to prescribe it so as to foster the specific modulations of CS excitability changes occurring during different phases of motor learning [10]. In particular, acute neuroplastic changes induced by a motor practice session decrease over a training period, and modulate subsequent changes in CS excitability induced by non-invasive brain stimulation protocols applied after a practice session [10]. In addition, cumulative effects of two facilitating paired-associative stimulation protocols applied successively did not result in an increase in CS excitability, but in depressed CS excitability [18]. These concurrent effects seem to be driven by

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homeostatic mechanisms, whereby the effect of physical exercise or non-invasive brain stimulation on neuroplasticity depends upon the neuroplastic changes induced by a precedent similar protocol [19]. This phenomenon could thus reverse the pro-excitability effect of a stimulation protocol [18] and makes it crucial to first decipher the effect of different types of exercise on neuroplasticity. Moreover, modulations of CS excitability by exercise are not region- or muscle specific and were reported in both exercised and remote (non-exercised) muscles.

1.1 Non-exercised muscles

Inconsistent changes in CS excitability of a remote hand muscle (increase [20]- or stability [21–24] have been reported following locomotor exercise. Despite few data, it seems that the mode of exercise – cycling vs running – might affect CS excitability, which increased following running exercise only [20]. Regardless of global CS excitability changes, studies using cycling consistently reported reduced cortical inhibition [21, 22, 25], and increased cortical facilitation [21, 24]. Such modifications in the balance between cortical facilitation and inhibition for a remote muscle make the case that locomotor exercise is a promising strategy to modulate neuroplasticity for motor learning purposes. As there is no data on the intracortical network changes induced by running, it remains to be determined whether the mode of locomotion influences neuroplastic changes occurring in a remote muscle.

1.2 Exercised muscles

Transient changes in excitability of the CS pathway have also been reported for muscles involved in exercise, yet they seem to depend on the features of the task performed. In most studies, CS excitability increased following submaximal single-joint tasks performed with the upper or the lower limb [25–27]. Nonetheless, similar exercises have led to unchanged [29], or depressed CS

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excitability when exercise was carried-out until exhaustion [30]. Single-joint exercises consistently depressed CS excitability and increased $GABA_B$ mediated cortical inhibition when conducted at maximal intensity (e.g. [30, 31].

Locomotor exercise, because it involves large muscle masses and leads to important hemodynamic solicitation, has the potential to significantly modulate CS excitability of exercised muscles [33]. It was indeed found that both maximal [34] and submaximal [34, 35] cycling exercise (from 30-s to 80-min) can increase CS excitability assessed in exercised muscles. Findings are however very heterogeneous: CS excitability was depressed at the end of an exercise at supra-maximal intensity, but unchanged at submaximal intensity [37]. Despite unchanged CS excitability, cortical inhibition either decreased following low-intensity pedalling [38, 39] or increased after exhaustive cycling at severe intensity [40], and decreased after pedaling until exhaustion at moderate intensity [40]. Such contrasting findings resulting from a wide variety of protocols limit our understanding of the effects of exercise characteristics on exercise-induced neuroplasticity. As recently emphasized by Mellow and colleagues [41], the diversity of experimental protocols makes it difficult to highlight any exercise characteristic primary influencing exercise-induced neuroplasticity [41]. For instance, the fatigue level induced by exercise directly affects CS excitability [40, 41]. It however seems that cardiorespiratory intensity is a key parameter that influences neuroplastic changes following locomotor exercise.

2. Exercise intensity affects hemodynamic processes underlying neuroplasticity

Mechanisms by which exercise triggers neuroplasticity may be linked with the increase in circulating neurotrophic factors (e.g. the Brain-Derived Neurotrophic Factor; BDNF) and hormones (e.g. Insulin-Growth Factor 1) in the systemic circulation, known to enhance cellular stress resistance in the brain [44]. BDNF and Insulin-Growth Factor 1 are released in the systemic

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148 blood circulation in response to muscle contraction [43, 44], and BDNF can also be secreted
149 directly by neurons in response to an increase in their activity [47]. Similarly to CS excitability
150 modulations, the greatest increases in muscle BDNF levels were reported following high-intensity
151 exercise [46, 47]. This intensity-dependent release of BDNF implies that practicing high-intensity
152 exercise could benefit neuroplasticity in healthy subjects [48]. Nonetheless, high-intensity exercise
153 also increases circulating levels of cortisol [50], a hormone known to impair neuroplasticity [51]
154 and cancel the benefits from BDNF. This might explain why pedaling intensity was shown to have
155 no influence on post-exercise CS excitability of a remote hand muscle [22, 50]. Even so, only high
156 exercise intensity decreased cortical inhibition immediately after exercise cessation [22].
157 Consequently, it seems that in order to benefit neuroplasticity, exercise intensity should be high
158 enough to increase BDNF levels, yet not too high in order to limit the release of cortisol.
159 Unfortunately, moderate or even high exercise intensity relative to one's limits, may not be enough
160 to induce neuroplasticity in deconditioned or symptom-limited individuals. Indeed, those with
161 neuromuscular or cardiorespiratory limitations may not be able to reach sufficient blood flow [53].
162 To circumvent this issue, studies investigated neuroplastic changes directly triggered by neural
163 mechanisms, at lower cardiorespiratory intensities.
164
165 ***3. Non-invasive stimulation studies hint at neural mechanisms of neuroplasticity***
166 Moderate intensity pedaling has been shown to cause neuroplastic changes when preceding non-
167 invasive brain stimulation protocols. For example, effects of paired-associative stimulation [52,
168 53] or theta burst stimulation [52] on CS excitability assessed in a remote hand muscle were
169 enhanced when preceded by low (~60% predicted maximal heart rate) to moderate (65 to 70%
170 predicted maximal heart rate) pedaling exercise. Other research groups demonstrated the influence
171 afferent muscle feedback exerts on acute neuroplasticity. Consistent findings also showed increases

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in CS excitability after the application of peripheral electrical stimulation designed to imitate muscular contraction [54, 55]. Authors suggested reduced cortical inhibition, or unmasked silent synaptic connections to explain increases in CS excitability [56]. In addition, the connectivity between the primary sensory and the primary motor cortex was likely increased, due to afferent inputs elicited by mixed influence of muscle contraction and sensations from electrical stimulation [57]. On the other hand, protocols that elicited nociceptive sensory stimulation without voluntary contraction, depressed CS excitability of the stimulated muscle [54–56], irrespective of stimulation frequency. Then, non-invasive muscle stimulation techniques appear to be efficient only when resembling muscle contraction.

Altogether, these results seem to indicate that locomotor exercise and non-invasive stimulation mainly trigger neuroplasticity via hemodynamic and neural processes, respectively. Even though combining the two methods allowed neuroplastic changes at moderate exercise intensity, the aforementioned drawbacks of stimulation techniques restrict the applicability of this approach. It is thus of greatest importance to find an alternative that is readily implementable yet provides similar benefits; locomotor eccentric exercise may prove useful.

4. Locomotor eccentric exercise to pool neural and hemodynamic neuroplastic processes

Certain individuals are unable to exercise at sufficient absolute cardiorespiratory intensities to trigger the hemodynamic mechanisms underlying neuroplastic adaptations. Eccentric exercise- an active lengthening of the muscle- may therefore allow to bypass this issue by a neural path towards neuroplasticity. Eccentric exercise is known for permitting to exercise at the same work rate than conventional exercise for a lower cardiorespiratory demand [57–59] and perceived effort [60–63]. Eccentric contractions also allow to perform tasks at moderate-to-high force levels while inducing limited muscle damage in pathological populations, such as individuals suffering from chronic

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obstructive pulmonary disease [64, 65] or obesity [66, 67]. In addition, the specific neural control of eccentric contractions could prove beneficial to neuroplasticity [68, 69]. When planning or executing eccentric muscle actions, the motor cortex is activated earlier, to a greater extent, and over a broader area than during concentric contraction- an active shortening of the muscle-[72]. Imagined eccentric actions also exhibited greater activity from pre-frontal brain regions compared with imagined concentric actions [73]. These specific cortical activities before movement onset would reflect the necessity of a greater neural control to perform eccentric actions [74]- probably serving to limit the mechanical strain exerted on the muscle-tendon complex in order to preserve it from damages [70, 71].

As conventional exercise, the features of eccentric exercise would influence its neuroplastic effect, specifically whether it involves only one of several joints. During eccentric single-joint [75] or locomotor [76] exercises, cortical activity was greater and cortical inhibition less [77] than during concentric contraction. Consistent findings also reported lower CS excitability in eccentric compared with concentric single-joint contractions [70, 76]. Greater spinal inhibition mediated by supraspinal mechanisms was thus proposed to regulate the motor command, in order to preserve the integrity of the muscle-tendon complex [76, 77]. The mode of muscle contraction did not affect CS excitability changes evaluated after elbow flexions [78, 79] or knee extensions [82]. Some authors measured reductions in cortical inhibition and increase in cortical facilitation immediately and until two hours after the completion of single-joint eccentric contractions [26, 78], and suggested it to be the consequence of an impaired motor control resulting from muscle damage [26, 81]. The long-lasting influence of eccentric contractions on cortical processes might also result from the greater motor control required to perform these tasks [80].

Less is known about how the mode of muscle contraction affects neuroplastic changes following locomotor exercises. But as aforementioned, locomotor eccentric exercise has the advantage of

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combining a challenging neural control with a low- but existing- hemodynamic solicitation. This might explain the increase in CS excitability in after running but not cycling mentioned earlier (see the section "*Physical exercise induces neuroplasticity*"), the latter exercise modality comprising short eccentric contractions. Despite this rationale, the mode of muscle contraction does not seem to affect the global changes in CS excitability of exercised lower limb or remote upper limb muscles, regardless of whether CS excitability increased [20, 57] or remained unaffected [23]. Locomotor eccentric exercise may nevertheless have the potential to stimulate brain plasticity in a way partly similar to motor training [10, 15]. In fact, studies from our laboratory suggested that decline walking could specifically modulate the excitability of transcerebellar sensory pathway when associated with paired-associative stimulation [20], and decrease cortical inhibition assessed in an exercised muscle when implemented alone [59]. The subsequent use of various exercise protocols during a training period could nonetheless yield distinct or opposite neuroplastic adaptations [19], depending on exercise features. The influence of locomotor eccentric exercise characteristics on neuroplasticity should thus be further studied.

Furthermore, eccentric cycling, whose effects on neuroplasticity are mostly unknown [23, 60], is increasingly available in rehabilitation centers. This exercise modality allows those unable to walk due to joint pathologies or obesity, to complete locomotor eccentric task. In addition to allowing force gains [84], and decreasing fat mass and increasing lean mass [68] while being well tolerated in patients [64, 83], eccentric cycling might enhance neuroplasticity and thus deserves its own set of investigations.

Conclusion

Conventional and eccentric locomotor exercises both showed beneficial neuroplastic effects similar to those associated to simple motor learning (i.e., decreased cortical inhibition and/or

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increase cortical facilitation). The changes induced by the former seem to originate from mainly hemodynamic mechanisms, while those triggered by the latter seem to be the result of neural, and maybe hemodynamic processes. Furthermore, the low cardiorespiratory response to eccentric contractions adds to the relevance of this exercise modality as an alternative to conventional rehabilitation protocols in weak patients. Future studies are nonetheless required to 1) describe the influence of conventional and locomotor eccentric exercise characteristics such as intensity, duration, or induced-fatigue, on the acute and chronic neuroplasticity, in order to optimise rehabilitation exercise protocols; 2) verify whether the hemodynamic solicitation of a locomotor eccentric exercise contributes to the resulting neuroplastic changes; and 3) look further into the neural hypothesis of eccentric exercise-induced neuromodulations, and try to fathom the respective influences of the complexity of the motor command and of the integration of muscle afferent feedback.

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Figure caption

Fig.1: Overview of the neuroplastic effects (assessed via changes in corticospinal excitability and activity of intracortical networks) of locomotor exercises and likely underlying mechanisms. Data related to conventional (i.e., concentric) and eccentric exercise are in blue and red font, respectively. Superscript numbers refer to the studies that provided the results featured below.

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Panel a: Summary of the neuroplastic effects for locomotor exercises (conventional vs eccentric) conducted at low, moderate (mod) or high cardiorespiratory intensity. # indicates that exercises were carried-out until exhaustion.

Panel b: Summary of the mechanisms (neural and/ or hemodynamic) suggested to induce neuroplasticity after each type of locomotor exercise.

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