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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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Abbreviations

BDNF: Brain-derived neurotrophic factor

BOLD: blood-oxygen-level-dependent

GABA: Gamma aminobutyric acid

IGF1: Insulin-growth factor 1

TMS: Transcranial magnetic stimulation

Abstract

Corticospinal excitability and particularly the balance between cortical inhibitory and excitatory processes (assessed in a muscle using transcranial magnetic stimulation), are affected by neurodegenerative pathologies or following a stroke. Non-fatiguing conventional locomotor exercise, such as cycling or walking, decreases intracortical inhibition and/or increases intracortical facilitation. These modifications notably seem to be a consequence of neurotrophic factors (e.g., brain-derived neurotrophic factors) resulting from hemodynamic solicitation. Furthermore, it can be inferred from non-invasive brain and peripheral stimulation studies that repeated activation of neural networks can endogenously shape neuroplasticity. Such mechanisms could also occur following eccentric exercises (i.e., active lengthening of the muscle), during which motor-related cortical potential is of greater magnitude and lasts longer (assessed by electroencephalography) than during concentric exercises (i.e., muscle shortening). As single-joint eccentric exercise decreased short- and long-interval intracortical inhibition and increased intracortical facilitation (assessed by paired-pulse transcranial magnetic stimulation immediately after), locomotor eccentric exercise may be even more potent by adding hemodynamic-related neuroplastic processes to endogenous processes. Besides, eccentric exercise is especially useful to develop relatively high force levels at low cardiorespiratory and perceived intensity, which can be a training goal in addition to inducing neuroplastic changes. Further studies are required to understand how neuroplasticity is 1) acutely influenced by locomotor exercise characteristics (e.g., intensity, duration), 2) modulated by an exercise-based rehabilitation program, 3) related to functional cognitive and motor outcomes relevant to pathological population.

Keywords

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

Introduction

During exercise, the primary motor cortex sends electrical impulses to trigger voluntary muscle contractions. The signal travels through nerves along the spinal cord (also termed corticospinal pathway), before reaching the alpha motoneuron, and then the muscle fibers it innervates. Corticospinal 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” (Weavil and Amann, 2018). For stimulation intensities 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 (Groppa et al., 2012). 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 (Farzan et al., 2013) and spinal (Škarabot et al., 2019b; Yacyshyn et al., 2016) levels. Paired-pulse TMS techniques also provide evidence that the recruitment of cortical neurons is mediated by inhibitory and facilitatory processes interacting at the cortical level (for a review see Chen, 2004). Particularly, the short-interval intracortical inhibition technique is thought to reflect the activity of gamma aminobutyric acid A ($GABA_A$) inhibitory neurotransmitters, while the long-interval intracortical inhibition technique, as well as the silent period duration (when lasting more than 100 ms), would reflect the activity of $GABA_B$ inhibitors (Chen, 2004). The intracortical facilitation technique informs on the activity of glutamatergic facilitatory networks (Chen, 2004). Any change in corticospinal excitability, cortical inhibition or facilitation would reflect the occurrence of neuroplastic processes (Mang et al., 2013), by which the central nervous system modifies its structure and functioning to encode new experience (Kleim and Jones, 2008). In particular, changes in the balance between cortical inhibition and facilitation could be a determinant of ontogenetic

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development (Gu, 2002), and is altered along with motor executive functions in individuals with neurodegenerative diseases (for a review see Vucic and Kiernan, 2017) or recovering from stroke (e.g. Dancause and Nudo, 2011; Hummel et al., 2009). Interestingly, this balance was also modified with motor learning (Rozenkrantz et al. 2007).

In this context, neurorehabilitation protocols using non-invasive stimulation techniques such as repetitive TMS or paired-associative stimulation have been developed in order to counteract deleterious neuroplasticity (Nitsche et al., 2012). Despite a growing interest for these methods over the past two decades, limitations such as their expensiveness and precautions of use in certain individuals (e.g., those with epilepsy) hinder their utilization in a wide population. Physical activity has thus been considered as a promising approach to modulate neuroplasticity in rehabilitation protocols.

This article provides a narrative review of 1) the impact of conventional locomotor exercise on neuroplasticity assessed in non-exercised or exercised muscles; 2) likely underlying neuroplastic processes triggered in relation with 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 exercise within this category, as a way to merge endogenous and hemodynamic-related neuroplastic mechanisms.

Physical exercise induces neuroplasticity

Physical exercise has consistently been reported as an efficient stimulus promoting neuroplasticity. Aerobic exercise notably reduces intracortical inhibition related to GABAergic concentration in a way similar to the leaning of a simple motor task (Floyer-Lea et al., 2006). This, among other phenomena such as an increase in the number of synapses in the motor cortex (Kleim and Jones, 2008), could have accounted for improved motor skill retention in patients with chronic stroke

(Nepveu et al., 2017) or Parkinson disease (Steib et al., 2018), when motor practice was implemented in addition to aerobic exercise.

It is nonetheless challenging to prescribe exercise in order for neuroplastic modulations to benefit patients, for at least five reasons: 1) Corticospinal responsiveness differs between populations (e.g., corticospinal excitability decreases and increases, in patients suffering from Huntington’s and Alzheimer’s diseases, respectively, (Vucic et al., 2011). Certain neuroplastic modulations could thus be beneficial to some populations but detrimental to others; 2) A given exercise may induce distinct neuroplastic modulations in two pathological populations; 3) Two facilitating paired-associative stimulation protocols applied successively had concurrent effects, depressing corticospinal excitability (Müller et al., 2007). These seem to be driven by homeostatic mechanisms, whereby the effects of physical exercise or non-invasive brain stimulation on neuroplasticity depends upon the effects induced by a precedent similar protocol (Abraham, 2008). Performing an exercise could thus reverse the pro-excitability effect of another; 4) In addition, inducing neuroplasticity is never the only focus of a physical exercise program; rather, prescription must aim for a compromise between targeted several outcomes (e.g., decreasing cortical inhibition, strengthening lower-limb muscles, improving respiratory fitness), 5) Finally, the influence of exercise characteristics (e.g., duration, intensity) on neuroplasticity remain unclear (Mellow et al., 2020).

Despite this last point, modulations of corticospinal excitability by exercise are not region- or muscle specific and were reported in both exercised and remote (non-exercised) muscles.

Transient changes in excitability of the corticospinal pathway have also been reported for muscles involved in exercise, yet they seem to depend on the features of the exercise performed. In most studies, corticospinal excitability increased following submaximal single-joint exercise performed with the upper- or lower-limb (Kotan et al., 2015; Pitman and Semmler, 2012; Williams et al., 2014). Nonetheless, similar exercises have led to unchanged (Finn et al., 2018), or depressed corticospinal excitability when exercise was carried-out until exhaustion (Brasil-Neto et al., 1993). Single-joint exercises have consistently depressed corticospinal excitability and increased silent period duration, when conducted at maximal intensity (e.g. Goodall et al., 2018; Kennedy et al., 2016).

Locomotor exercise, because it involves large muscle masses and leads to important hemodynamic solicitation, has the potential to significantly modulate corticospinal excitability of exercised muscles (Sidhu et al., 2013). It was indeed found that both maximal (Fernandez-del-Olmo et al., 2013) and submaximal (Jubeau et al., 2014; Temesi et al., 2013) cycling exercise (from 30-s to 80-min) can increase corticospinal excitability, assessed in exercised muscles. Findings are however very heterogeneous: corticospinal excitability was depressed at the end of an exercise at supra-maximal intensity, but unchanged at submaximal intensity (80% peak power output, Sidhu et al., 2012). Despite unchanged corticospinal excitability, short-interval intracortical inhibition either decreased immediately following self-selected low-intensity pedaling (Yamaguchi et al., 2012; Yamazaki et al., 2019), increased after exhaustive cycling at severe intensity- although the silent period was shorter- (92% peak oxygen uptake; O'Leary et al., 2016), or decreased after pedaling until exhaustion at moderate intensity (52% peak oxygen uptake; O'Leary et al., 2016).

Corticospinal excitability, assessed in a remote hand muscle was unchanged following cycling (Morris et al., 2019; Singh et al., 2014a; Smith et al., 2014; Walsh et al., 2019), but increased after running (Garnier et al., 2017). It thus seems that the mode of exercise – cycling vs running – might affect corticospinal excitability, yet more evidence is needed. All cycling studies, reported reduced short-interval intracortical inhibition (Singh et al., 2014a; Smith et al., 2014), and increased intracortical facilitation (Morris et al., 2019; Singh et al., 2014a) examined by paired-pulse TMS. 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 recently emphasized (Mellow et al., 2020), the diversity of experimental protocols makes it difficult to highlight any exercise characteristic primary influencing exercise-induced neuroplasticity. For instance, an exercise causing significant fatigue typically diminishes corticospinal excitability by reducing motoneurons responsiveness and increasing inhibitory nociceptive afferent feedback (Gandevia, 2001), masking the effects other characteristics such as exercise intensity may have following a shorter exercise (i.e., too short to cause significant fatigue). In however seems that cardiorespiratory intensity is a key parameter that influences neuroplastic changes following locomotor exercise.

Exercise intensity affects hemodynamic-related 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 (van Praag et al., 2014). BDNF and Insulin-growth factor 1 are released in the systemic blood circulation in response to muscle contraction (Berg and Bang, 2004; Matthews et al., 2009). BDNF can also be secreted directly by neurons in response to an increase in their activity, yet whether muscle BDNF somehow passes the brain-blood barrier or if the brain produces all the BDNF concentrated in its tissues remains unclear (Marie et al., 2018).

Similar to corticospinal excitability modulations, the greatest increases in muscle BDNF levels were reported following high-intensity exercises (Knaepen et al., 2010). A likely explanation is that high-intensity exercise is accompanied by a proportional important blood flow and endothelial shear stress, responsible for BDNF release (Cefis et al., 2019). While high-intensity exercise could

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prompt neuroplasticity in healthy subject, it can also increase circulating levels of cortisol (Rojas Vega et al., 2006), a hormone known to impair neuroplasticity (Sale et al., 2008) and hinder the effects from BDNF. This might explain why pedaling intensity was shown to have no influence on post-exercise corticospinal excitability of a remote hand muscle (McDonnell et al., 2013; Smith et al., 2014). Consequently, it seems that in order to promote neuroplasticity, exercise intensity should be high enough to increase BDNF levels, yet not too high in order to limit the release of cortisol. Even so, only high exercise intensities (80% of heart rate reserve) decreased short-interval intracortical inhibition immediately after exercise cessation (Smith et al., 2014). While symptom-limited individuals are unable to exercise at a sufficient intensity to achieve a relatively high blood flow (Barak et al., 2017), they seem to release significant amounts of BDNF at low intensity levels (Knaepen et al., 2010).

It is possible to induce neuroplastic changes directly via endogenous mechanisms (i.e., resulting from repeated activation of neural networks), at low cardiorespiratory intensities. The presence of such mechanisms is evidenced by non-invasive stimulation studies (see section "*Non-invasive stimulation studies hint at endogenous mechanisms of neuroplasticity*"), and it may be possible to take advantage of them using eccentric exercise, which is already employed as a rehabilitation tool for other reasons (see section "Locomotor eccentric exercise to pool endogenous and hemodynamic-related neuroplastic processes").

Non-invasive stimulation studies hint at endogenous mechanisms of neuroplasticity

Moderate intensity pedaling has been shown to promote neuroplasticity when preceding non-invasive brain stimulation protocols. For example, effects of paired-associative stimulation (Mang et al., 2014; Singh et al., 2014b) or theta burst stimulation (McDonnell et al., 2013) on corticospinal excitability assessed in a remote hand muscle were enhanced when preceded by low (~60%

predicted maximal heart rate) to moderate (65 to 70% predicted maximal heart rate) pedaling exercise. Other research groups demonstrated the influence afferent muscle feedback exerts on acute neuroplasticity, namely increases in corticospinal excitability after the application of peripheral electrical stimulation designed to imitate muscular contraction (Chipchase et al., 2011; Schabrun et al., 2012). Authors have proposed reduced cortical inhibition, or unmasked silent synaptic connections to explain this modification (Chipchase et al., 2011). 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 (Schabrun et al., 2012). On the other hand, protocols that elicited nociceptive sensory stimulation without voluntary contraction, depressed corticospinal excitability of the stimulated muscle (Chipchase et al., 2011; Mang et al., 2010; Schabrun et al., 2012), irrespective of stimulation frequency.

Altogether, these results seem to indicate that locomotor exercise and non-invasive stimulation mainly trigger neuroplasticity via hemodynamic-related processes or repeated activation of exercise-related neural networks, respectively. Even though combining the two methods allowed neuroplastic changes at moderate exercise intensities, the aforementioned drawbacks of stimulation techniques restrict the applicability of this approach. It is thus of greatest importance to find a readily implementable method providing similar benefits; eccentric exercise (i.e., an active lengthening of the muscle), especially when locomotor, may prove efficient.

Locomotor eccentric exercise to pool endogenous and hemodynamic-related neuroplastic processes?

Eccentric exercise may be an alternative to conventional exercise, inducing neuroplasticity through endogenous mechanisms. It is known to elicit a lower cardiorespiratory demand (Abbott et al., 1952; Garnier et al., 2019; Lemire et al., 2019) and perceived effort (Clos et al., 2019; Elmer and Martin, 2010) than conventional exercise at the same work rate. It has also been shown to induce limited muscle damage in pathological populations, such as individuals suffering from chronic obstructive pulmonary disease (Pageaux et al., 2019; Vieira et al., 2011) or obesity (Julian et al., 2018; Thomazo et al., 2019), while exercising at high-to-moderate force levels. In addition, the "challenging" brain control of eccentric contractions (Perrey, 2018) could foster neuroplasticity. Indeed, when executing eccentric contractions, the movement-related cortical potential, as assessed using electroencephalography, was of greater magnitude and started earlier before the movement (Fang et al., 2004, 2001) than when performing concentric contractions. Other studies reported greater rises in blood-oxygen-level-dependent (BOLD) signal in the primary sensory cortex (Yue et al., 2000) and in the supplementary motor area (Kwon and Park, 2011) during wrist flexion movement, or in pre-frontal cortex during imagined eccentric than concentric elbow flexions (Olsson et al., 2012). Finally, near-infraread spectroscopy revealed a greater activation of the contralateral primary motor cortex during eccentric than concentric elbow flexions (Borot et al., 2018). These specific cortical activations before the onset of movement were proposed to have a role in limiting the mechanical strain exerted on the muscle-tendon complex in order to preserve it from damage (Fang et al., 2004; Olsson et al., 2012).

As for conventional exercise, the features (e.g, volume, intensity) of eccentric exercise likely influence the way it modulates corticospinal excitability, notably whether the exercise involves a single joint or is locomotor.

Short-interval intracortical inhibition was lower during eccentric than concentric index finger abduction (Opie and Semmler, 2016). Consistent findings also reported lower corticospinal excitability in eccentric compared with concentric single-joint contractions (Fang et al., 2004; Sekiguchi et al., 2003). Greater spinal inhibition, mediated by supraspinal mechanisms, was thus

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proposed to regulate the motor command, again in order to preserve the integrity of the muscle-tendon complex (Sekiguchi et al., 2003, 2001). The mode of muscle contraction did not affect corticospinal excitability changes evaluated after elbow flexions (Latella et al., 2018; Löscher and Nordlund, 2002) or knee extensions (Clos et al., 2020; Garnier et al., 2018). Some authors nevertheless reported reductions in short-interval intracortical inhibition (lasting two hours, Pitman and Semmler, 2012), long-interval intracortical inhibition and silent period duration (Škarabot et al., 2019a), and increases in intracortical facilitation (lasting one hour Latella et al., 2018). These changes were suggested to be the consequence of an impaired motor control resulting from muscle damage (Pitman and Semmler, 2012; Škarabot et al., 2019a). The long-lasting influence of eccentric contractions on cortical processes might also result from the complexity of the motor control required to perform these exercises- greater than for concentric contractions (Latella et al., 2018).

Less is known about how the mode of muscle contraction affects neuroplastic changes following locomotor eccentric exercise, which should combine a longer and more pronounced activation of motor and sensory cortical networks than its concentric counterpart (as shown in single-joint exercises), with a low- but potentially significant- hemodynamic solicitation. Despite this rationale, the mode of muscle contraction does not seem to affect the global changes in corticospinal excitability measured in exercised lower limb or remote upper limb muscles, regardless of whether corticospinal excitability increased (Garnier et al., 2019, 2017) or remained unaffected (Walsh et al., 2019). Locomotor eccentric exercise may nevertheless have the potential to stimulate brain plasticity in a way partly similar to motor learning (Floyer-Lea et al., 2006; Rosenkranz et al., 2007). 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 (Garnier et al., 2017), and decrease short-interval intracortical inhibition assessed in an exercised muscle when implemented alone (Garnier et al., 2019). Furthermore, eccentric cycling, whose effects on neuroplasticity are mostly unknown (Clos et al., 2019; Walsh et al., 2019), is increasingly available in rehabilitation centers. This exercise modality allows those unable to walk due to joint pathologies or obesity, to complete locomotor eccentric exercises. In addition to allowing force gains (Hoppeler, 2016), and decreasing fat mass and increasing lean mass (Julian et al., 2018) while being well tolerated in patients (LaStayo et al., 2013; Pageaux et al., 2019), eccentric cycling might enhance neuroplasticity and thus deserves its own set of investigations.

Conclusion

Conventional and eccentric locomotor exercises can both lead to decreases in intracortical inhibition and increases in intracortical facilitation, which is also the case of the learning of a basic motor task. The changes induced by conventional exercise seem to originate mainly from hemodynamic mechanisms causing the release of neurotrophic factors, while those triggered by locomotor eccentric exercise seem to be the result of repeated activation of neural networks, and maybe of hemodynamic processes as well. 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. Regardless of the strategy employed, the assessment of locomotor exercise-induced neuroplasticity is seldom accompanied by a functional evaluation (e.g., cognitive or motor task), and the influence of a locomotor exercise program alone (i.e., without associated stimulation) on the plasticity of brain neural networks has not been tested. These two aspects should be investigated. In addition, future studies should further describe the influence of conventional and locomotor eccentric exercise characteristics such as intensity,

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duration, or induced-fatigue (related to training status), in order to optimize clinical exercise protocols.

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Figures

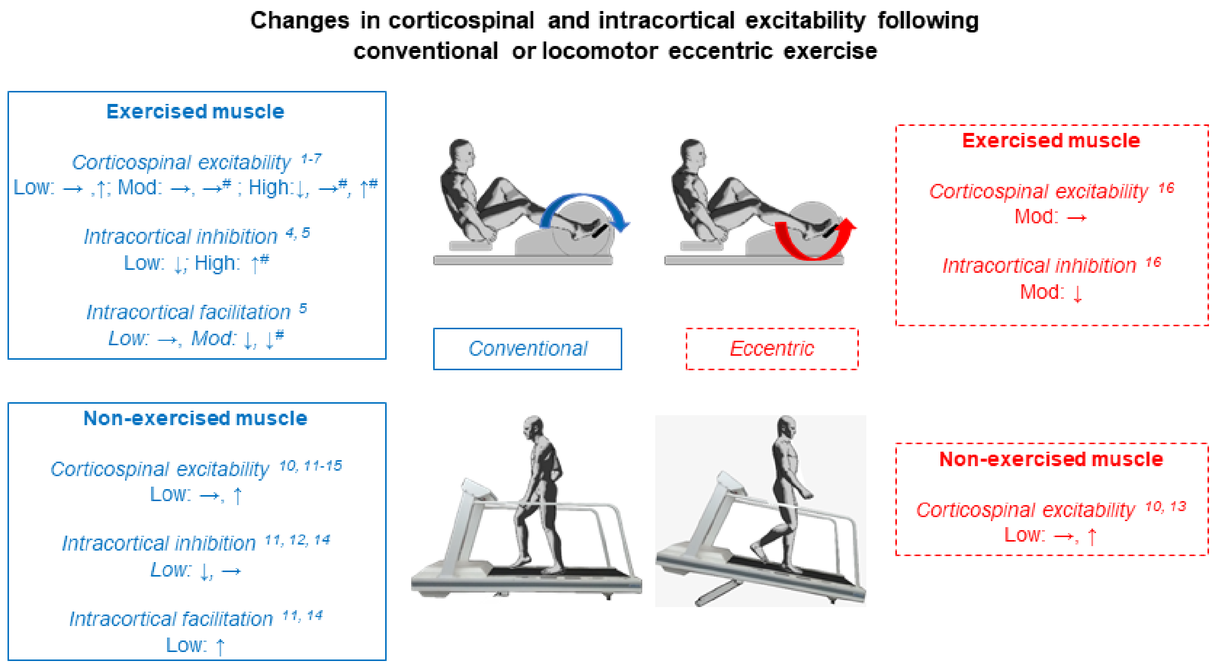

Fig.1: Overview of the neuroplastic effects (assessed via changes in corticospinal excitability and activity of intracortical networks) of locomotor exercises. Data related to conventional (i.e., concentric) and eccentric exercise are in blue and red font, respectively. Superscript numbers refer to the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

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.

Reference numbers: 1: Fernandez-del-Olmo et al. (2013), Scand. J. Med. Sci. Sports; 2: Jubeau et al. (2014), PLoS One; 3: Temesi et al. (2013), Med. Sci. Sports Ex.; 4: Sidhu et al. (2012), J Neurophysiol; 5: Yamaguchi et al. (2012), Exp. Brain Res.; 6: Yamakazi et al. (2019), Front Physiol; 7: O'Leary et al. (2016), Scand. J. Med. Sci. Sports; 8: Pitman and Semmler (2012), J App Physiol; 9: Williams et al. (2014), PLoS One; 10: Garnier et al. (2017), Brain Behav. Res.; 11: Singh et al. (2014), BMC Sports Sci. Med. Rehabil; 12: Smith et al. (2014), Exp. Brain Res.; 13: Walsh et al. (2019), Sci. Rep; 14: Morris et al. (2019), Eur. J. Neurosci; 15: Mang et al. (2016) ; 16: Garnier et al. (2019), Exp. Brain Res.

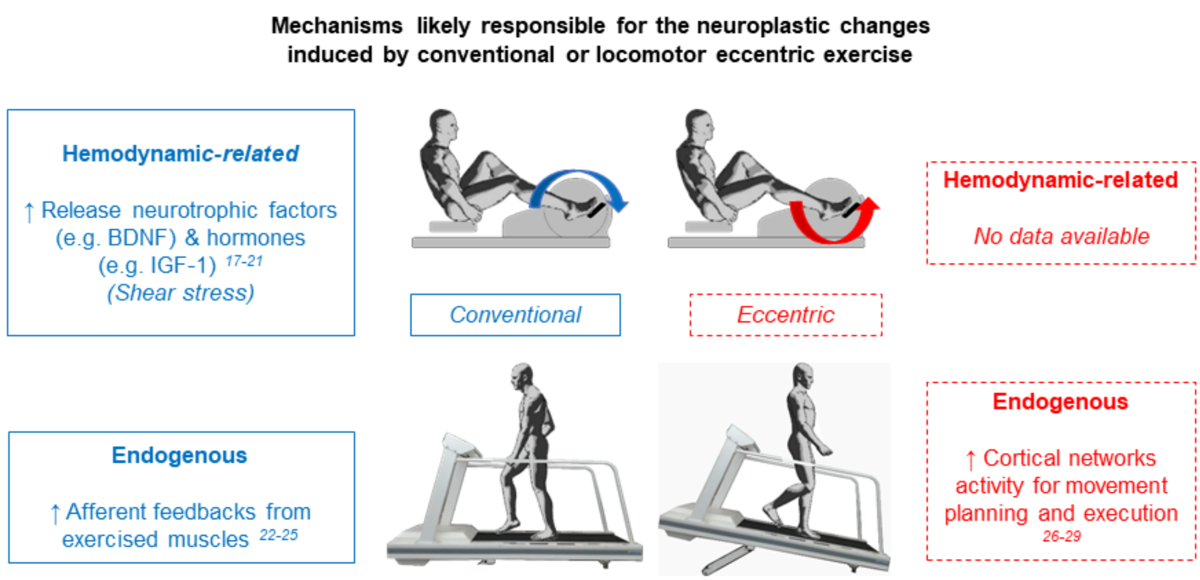

Fig.2: Summary of the mechanisms (endogenous and/ or hemodynamic-related) suggested to induce neuroplasticity after each type of locomotor exercise. Data related to conventional (i.e.,

concentric) and eccentric exercise are in blue and red font, respectively. Superscript numbers refer to the studies that provided the results featured below.

Reference numbers: Neural Plast; 17: Berg and Bang (2004), Horm. Res; 18: Matthews et al. (2009), Diabetologia; 19: Marie et al. (2018), J. Cereb. Blood Flow Metab;; 20: Knaepen et al. (2010), Sports Med.; 21: Céfis et al. (2019), Brain Struct. Funct.; 22: Mang et al. (2014), JAP; 23: Singh et al. (2014), Exp. Brain Res.; 24: Chipchase et al. (2011), Arch. Phys. Med. Rehabil; 25: Schabrun et al. (2012), PLoS One; Exp. Brain Res.; 26: Fang et al. (2004), Brain Res.; 27: Olsson et al. (2012), Front. Hum. Neurosci; 28: Fang et al. (2001), J. Neurophysiol; 29: Borot et al. (2018), Brain Sci.

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