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## ***EDITORIAL***

Boosting brain motor plasticity with physical exercise

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Neuroplasticity is a fundamental process that occurs within the central nervous system during learning of a new ability for example, or more generally when internal or environmental conditions are modified. Neuroplasticity involves both functional and structural changes and may help functional recovery when neuronal networks have been damaged (following brain or spinal cord injury or a peripheral nerve lesion) or when afferent or efferent modules of a system are damaged (e.g. sensory loss, limb amputation). One of the challenging and topical issues of neurosciences is to better understand the highly complex mechanisms of neuroplasticity and to become able to augment these when necessary.

Motor cortex plasticity can be influenced by many different factors and interventional procedures such as rehabilitation, physical exercise or non-invasive transcranial brain stimulation (NIBS), and it is likely that combining these various interventions could have a synergistic impact for inducing brain plasticity. For example, NIBS protocols have been used successfully in stroke patients to facilitate the effects of subsequent physiotherapy [5]. How the different protocols can be paired for maximizing plasticity and its underlying mechanisms is, so far, not well understood.

Repetitive Transcranial Magnetic Stimulation (rTMS), theta-burst stimulation (TBS), Paired-Associative Stimulation (PAS) or transcranial Direct or Alternative Current Stimulation (tDCS or tACS respectively) are different kinds of NIBS methods that are becoming more and more widely employed to increase or decrease cortical excitability (depending on the stimulation pattern used) for minutes or even hours. Low frequency rTMS (<1Hz) and continuous TBS, applied over the primary motor cortex (M1), exert an inhibitory effect on neurons of the corticospinal tract, as assessed by the decrease of motor potential amplitude, recorded in the targeted muscles. In contrast, patterned

stimulation, i.e. high frequency bursts separated by periods without stimulation (high frequency rTMS and intermittent TBS), lead to increased corticomotor excitability. Indirect evidence suggests that continuous and patterned NIBS train stimulations exert synaptic effects similar to long term-depression (LTD) or long-term potentiation (LTP), respectively, as observed in cortical slices [21]. Paired-associative protocols are derived from animal experiments showing that LTP may occur when pre- and post-synaptic elements are stimulated with precise timing, whereas LTD is observed when the same stimuli are not time-locked. In accordance with this spike timing-dependent plasticity rule, changes in corticomotor excitability can be obtained by pairing a peripheral electrical stimulation with one TMS pulse over the contralateral M1 area. The repetition of these doublets every 10-20 seconds for at least 15min induces a directional effect on corticomotor excitability, depending on the inter-stimulus interval : LTP-like effect for ISI around 25 ms and LTD-like effect for ISI of 10ms [20]. In contrast with rTMS, TBS or PAS that produce neuronal firing, tDCS and tACS exert an effect on the membrane potential, tending to shift this toward hyper- or depolarisation, depending on current direction (anodal vs cathodal). An important finding is that the NIBS effect on brain excitability in humans strongly depends on the neural background activity prior to the stimulation, as stated by the Bienenstock–Cooper–Munro (BCM) rule of synaptic plasticity. For example, the net inhibitory influence of low frequency rTMS can be suppressed or even reversed to facilitation when the basal level of neural activity is raised beforehand by an anodal tDCS [13]. This homeostatic meta-plasticity has been suggested to stabilise the neural networks within an operational range of synaptic changes and to prevent uncontrolled positive feedback processes during skill learning, for example.

Whatever the NIBS protocol employed to induce neuroplasticity, changes of corticomotor excitability lasting beyond the time of stimulation can be observed, but the effects are often modest and not consistent from one subject to another. Though the usefulness of NIBS to induce neuroplasticity in neurological diseases is not questioned ([9] for a review), enhancing effects of NIBS represents an exciting and essential challenge in neuroscience. In this context, priming NIBS with physical activity may be an efficient and convenient manner to boost neuroplasticity.

In animals, the role of physical activity has been evidenced in molecular signalling pathways involved in brain plasticity [1] and in the increase of neurotrophic factors such as Brain Derived Neurotrophic Factor (BDNF) accompanying axonal growth, after peripheral nerve crush injury [12]. In rats, wheel running is also accompanied by structural changes, such as increased rate of neurogenesis and angiogenesis, as well as greater dendritic spine density (for review, see [8]). Many changes also occur at the cerebral level in the neurotransmitter system which is known to play a crucial role in neuroplasticity. In humans, structural changes were observed in the white and grey matter of older people who underwent regular physical activity [4]. As in rodents, physical exercise in humans also induces molecular and cellular changes, such as increased BDNF, or decreased GABA-A transmission [17][14][19]. Because the rTMS-induced level of LTP- LTD-like plasticity has been suggested to depend on polymorphisms of the BDNF gene [2] and also on GABA transmission, it could thus be considered that physical exercise may prepare the brain for subsequent NIBS protocols.

In line with this hypothesis, a few studies have been conducted in the last decade to look at the effects of exercise and NIBS-induced corticomotor plasticity. Cirillo and colleagues [3] were the first to report that, compared with sedentary subjects, active adults

(according to the International Physical Activity Questionnaire) were more receptive to an excitatory PAS protocol. Interestingly, Cirillo and co-workers pointed out that the PAS-induced increase of neuroplasticity was observed in the M1 region controlling the finger muscles, whereas the aerobic activities performed by the active subjects, such as cycling or running, involved the lower limbs. In other words, the influence of physical exercise on the sensorimotor system was broad, i.e. not restricted to the motor region specifically involved in the control of the muscles needed by the physical exercise.

Another recent and promising finding is that a short period of aerobic exercise seems to be sufficient to promote NIBS induced plasticity. For example, a single bout of low-level aerobic pedalling exercise (at 57% of the age predicted maximum heart rate) increased the down-regulatory effect of continuous TBS on corticomotor excitability in circuits controlling the hand muscles [11]. The effect of acute exercise on LTP-like plasticity has also been studied, producing contrasting results. Singh et al [15] reported an increase in the M1 excitability of hand muscles after a PAS protocol preceded by aerobic cycling exercises at moderate intensity, compared to PAS alone. This increase of the LTP-like effect was also reported following high intensity, intermittent exercise, by Mang et al [10] who measured PAS-induced changes in corticomotor excitability. In contrast, it was recently shown that after a single bout of a continuous pedalling exercise at high intensity, the net influence of intermittent TBS was a decrease in motor cortex excitability, instead of the expected increase [18].

To date, the mechanisms by which aerobic exercise may promote NIBS protocols remain unclear and are likely to be multifactorial with intermingled effects of cortisol, BDNF (and other neurotrophins), changes in GABAergic transmissions and other neurotransmitters (such as dopamine, norepinephrine or serotonin) at the cortical level.

Increase in BDNF serum concentration with physical exercise has been suspected to be a key element. However, NIBS-induced plasticity increases after low level exercise, even when BDNF serum level does not change [11], and there is no evidence for a correlation between individual BDNF serum levels after exercise and PAS-induced LTP-like effect [10]. Induction of LTP in the motor cortex is strongly dependent on the reduction of GABAergic transmissions, as evidenced by Hess and Donoghue [7] who showed in rats that LTP occurred following TBS when bicuculline, an antagonist of GABA-A receptors, was applied prior to stimulation. In humans, physical exercise is also accompanied by the reduction of short latency intracortical inhibition (SICI) [14][19], a mechanism which depends on GABA-A receptors [5] and this lowering of GABA inhibition has been suggested to participate, at least in part, in the increase of NIBS-induced plasticity following exercise (for a review see [16]).

Taken together, these studies converge toward the idea that physical exercise has the capacity to promote plasticity in the motor cortex. These findings open new opportunities for physiotherapists to increase the efficacy of rehabilitation, since for example, even a single session of exercise (such as 20 minutes of biking at a moderate rate) is likely to increase brain responsiveness to motor rehabilitation techniques.

In their review of the literature about the synergistic action of aerobic exercise and NIBS protocols, Hendrikse et al [6] pointed out that, because aerobic exercise has a broad impact on brain circuits with widespread neurogenic and neurotrophic effects, it can also be used to enhance NIBS effects in non-motor regions, to improve cognitive function for example, or more generally to increase brain responsiveness to NIBS protocols in neurological diseases. In pharmacoresistant depression for example,

aerobic exercise could be performed before NIBS over the dorsolateral prefrontal cortex to increase its effects.

However, to date, the literature is rather scarce and shows great variability in terms of outcome measures, the kind of physical exercise and NIBS protocols. Future studies are therefore essential to consider the clinical usefulness of physical exercise. An important challenge is to better understand the mechanisms involved in the potential effect of exercise (in particular the role of BDNF, neurotransmitters, cortisol and lactates), and to determine the protocol able to maximise NIBS, or motor rehabilitation, with exercise.

**Conflicts of interest:** none

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