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Can cerebellar transcranial direct current stimulation become a valuable neurorehabilitation intervention?

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Noninvasive brain stimulation techniques have had a very important role in the field of neurological rehabilitation. Transcranial magnetic stimulation (TMS) has been used successfully for the last 20 years to help understand some of the mechanisms underlying motor recovery when humans experience brain lesions, such as stroke [1]. This information has more recently been turned into therapeutic targets for the application of TMS to induce or facilitate plastic changes associated with behavior, and in turn to enhance performance. In the last 10 years, a second technique, transcranial direct current stimulation (tDCS), has been resuscitated (this tool was under-used for almost two decades) and refined to become a widely used neuromodulatory strategy for investigating brain physiology and modulating behavior [2]. Currently, there is little doubt in the neurological rehabilitation field that these techniques will eventually play a therapeutic role in the recovery process following brain lesions. It is only a matter of time until large, well-designed clinical trials demonstrate their true value in the clinical setting. However, which brain regions need to be stimulated to optimize effects on behavior and recovery is an important consideration these trials will have to address, among others (i.e., dose, the type of location, timing after stroke and others).

So far, most of the research investigating the mechanism of motor recovery following stroke has focused on the role of the primary motor cortices (either ipsilesional or contralesional) and premotor areas [3]. These studies have tested the type of excitability changes that occur following stroke, connectivity changes at rest and in the context of movement performance and the potential usefulness of neuromodulatory techniques to improve motor behavior. Targeting primary and secondary motor areas with brain stimulation makes sense because of the obvious role these regions have in motor behavior. However, the cerebellum, a critical

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neural structure for motor control and learning [4], has received relatively little attention so far. This is not due to the fact that the cerebellum is in the back of the head, but rather to the challenges of stimulating it noninvasively and being able to read out the effects of the stimulation.

Since the 1990s, Ugawa *et al.* have shown that it is possible to stimulate the cerebellum and measure its effects via modulation of primary motor cortex (M1) responses [5,6]. Using a TMS paired pulse technique, a motor evoked potential elicited from M1 is inhibited by a conditioning stimulus applied over the cerebellum 5–7 ms before M1 stimulation. This measurement, known as cerebellar brain inhibition (CBI), has been interpreted as an activation of Purkinje cells in the cerebellar cortex. Given that the dentate has disynaptic excitatory connections with the motor cortex (dentate–thalamo–cortical pathway) [7], inhibition of the dentate nucleus by Purkinje cell activation results in inhibition of M1. Other studies have addressed the physiological role of the cerebellum indirectly, by investigating the excitability changes that occur in M1 as a consequence of cerebellar lesions [8]. However, not until recently have we been able to show how cerebellar excitability changes with behavior.

Animal and human lesion studies have shown that the cerebellum is crucially involved in motor learning. Therefore, the first demonstration that we can measure cerebellar excitability changes in humans had to be tied to a motor learning paradigm. Using a locomotor learning task known to involve the cerebellum (a patient with cerebellar degeneration cannot learn this task) [9], we have shown that the inhibitory tone the cerebellum exerts over M1 at rest is reduced proportional to the magnitude of learning [10]. This finding is consistent with animal literature demonstrating a decreased Purkinje cell drive in association with learning [11]. Interestingly, although M1 excitability also changed, this effect was not learning-specific and was rather associated with the execution of the locomotor task. Recently, we have found a similar cerebellar excitability effect when individuals learn a reaching adaptive motor task with their arm [12]. Interestingly, the changes in cerebellar–M1 connectivity were present during the steepest learning phase, but return to baseline levels as subjects approached asymptote. These findings demonstrate that it is feasible to measure cerebellar excitability during human behavior, and that we can study how the cerebellum changes in association with motor learning. Perhaps more importantly, they provide a target for neuromodulatory techniques to manipulate cerebellar excitability and behavior.

In the last few years, research using noninvasive stimulation techniques has shown that it is possible not only to measure, but also to modulate cerebellar activity in humans. For instance, application of tDCS over the cerebellum results in excitability changes in a polarity-specific manner [13]. In particular, this study showed that anodal cerebellar tDCS increased the inhibitory tone the cerebellum exerts over M1 (CBI), whereas cathodal tDCS had the opposite effect. Other studies assessed the consequence of modulating cerebellar excitability indirectly by measuring plastic changes occurring in M1 when repetitive TMS was delivered over the cerebellum [14] or when tDCS was applied over the cerebellum of rats with cerebellar lesions [15]. Finally, another recent study showed that it is possible to affect cerebellar excitability with tDCS as indicated by inhibition of plasticity changes

occurring in the sensorimotor cortex [16]. Altogether, these investigations demonstrate that it is possible to modulate the excitability of the cerebellum, creating an opportunity to test whether noninvasive cerebellar stimulation can affect human motor behavior.

Although it is clear that tDCS can be used to modulate cerebellar activity, to date, few studies have investigated the effects of this modulation on behavior. Research in the motor domain has shown that anodal cerebellar tDCS can enhance learning. Using the same locomotor learning paradigm utilized to demonstrate cerebellar excitability changes, Jayaram *et al.* found that anodal tDCS sped up the acquisition of a new walking pattern whereas cathodal stimulation slowed it down [17]. Similarly, Galea *et al.* showed that anodal tDCS applied over the cerebellum during a reaching adaptation task facilitated learning [18]. Of note, these studies in healthy individuals did not induce behavioral changes during simple reaches or normal treadmill walking. This suggests that when the system is challenged (i.e., adapting to a perturbation that would otherwise elicit performance errors), cerebellar stimulation can have an effect on behavior, but not when the task is overpracticed. Future investigations will need to determine whether cerebellar lesions (i.e., cerebellar degeneration) also represent a challenge to the system that can benefit from cerebellar stimulation.

The cerebellum has been recognized as an important structure for cognitive [19] and emotional functions [20] that go beyond the motor domain, and these functions can also be affected by direct current stimulation. For instance, an early study showed that cerebellar tDCS could affect working memory on a visual cognitive task (Sternberg test) [21]. Recently, another study investigated the role of the cerebellum in working memory and attention during performance of different cognitive tasks, the Paced Auditory Serial Addition Task and a more challenging variant called the Paced Auditory Serial Subtraction Task. The investigators found a cathode-specific effect where only the performance of the more difficult task improved relative to anodal and sham stimulation. These findings were interpreted to be mediated by a disinhibition of prefrontal areas when cerebellar excitability was reduced with cathodal tDCS [22]. Finally, another study investigated the effects of cerebellar tDCS on the recognition of emotional facial expressions and found that tDCS improved the ability to recognize negative facial expressions [23]. The authors suggested a modulation of cerebellar–amygdala connections as a potential substrate.

Altogether, the aforementioned studies are very important not only because they inform us about the role of the cerebellum in different tasks, but also because they suggest that direct current stimulation over the cerebellum can modulate behavior in healthy individuals. These promising results beg the question of whether it is possible to augment behavior in patients with neurological lesions via cerebellar tDCS. This would lead to the development of this intervention as a therapeutic tool in neurorehabilitation. Importantly, future research will have to address questions at two different levels. First, given that performance of a task involves multiple processes (i.e., during motor learning one can modulate acquisition via cerebellar tDCS vs retention via M1 tDCS), what is the more advantageous process to target in order to obtain the best behavioral outcome? Second, to enhance behavior or recovery of neurological patients, what is the most beneficial approach when choosing a stimulation site:

to enhance the activation of a partially damaged region or to enhance the function of nondamaged areas with the goal of facilitating compensation?

In summary, investigations applying direct current stimulation over the cerebellum have shown interesting results. Early studies indicate that it is possible to modulate cerebellar activity and that this form of stimulation can elicit behavioral effects in the motor and cognitive domains. These findings are not only relevant to our understanding of neuroscience, but also suggest that this approach has a potential therapeutic role in the field of neurological rehabilitation.

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