Cerebellum (2017) 16:276–278
DOI 10.1007/s12311-016-0768-y

LETTER TO THE EDITOR

Transcranial Non-Invasive Brain Stimulation in Parkinson's Disease Patients with Dyskinesias. Where is the Optimal Target?

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Published online: 1 March 2016

Dear Editor,

The treatment of secondary effects of levodopa treatments in Parkinson's disease (PD) patients is an actual necessity and priority in clinical practice. The paper made by Ferrucci et al. [1] represents an additional confirmation that levodopa-induced dyskinesias (LIDs) are potentially treatable by neuromodulation techniques. Differently from previous literature, this is the first study using transcranial direct current stimulation (tDCS) to reduce dyskinetic movements in PD. Indeed, until now, nine papers had provided evidence on the effectiveness of non-invasive brain stimulation (NIBS) administered as repetitive transcranial magnetic stimulation (rTMS). However, despite methodological and technical differences (tDCS vs. rTMS; single vs. prolonged stimulation sessions; inhibitory vs. excitatory; and unilateral vs. bilateral) what merits to be focused after the current article is *where* stimulation should be applied. In other words, which is the main brain region to be targeted in LIDs patients: the Motor Cortex? Supplementary Motor Area (SMA)? Cerebellum? Or Inferior Frontal Cortex (IFC)?

The target location problem in LIDs is strongly dependent upon the current pathophysiological model. In the last few years, a considerable effort has been made to understand the neurobiological basis of this motor complication. LIDs are classically ascribed to the degree of nigrostriatal neurodegeneration and striatal changes associated with chronic levodopa therapy [2]. These interact to induce maladaptive striatal plasticity, which has the effect of altering neuronal activity in striatopallidal circuits. The first step in imaging of LIDs was made by Rascol [3] and Brooks [4], who demonstrated that these abnormal neuronal firing patterns extended on the brain cortex mainly including the sensorimotor areas of the cortico-basal ganglia loop. Guided by these first neurofunctional results, neuromodulation over regions showing functional overactivity in LIDs was tested either for the primary motor cortex (M1) [4–10] or for the SMA [11, 12].

Although, Ferrucci et al. [1] demonstrated that non-invasive brain stimulation over the M1 improved LIDs, the present literature is characterized by conflicting findings. First of all, Wagle-Shukla et al. [5], by using a prolonged session (2 weeks) of low frequency (1HZ) rTMS, reported no evident clinical improvements in six PD patients with LIDs. This preliminary lack of significant effects has also been confirmed in two recent studies [6, 10], despite the employment of different rTMS protocols. Otherwise, three additional studies demonstrated moderate evidence about the role of the M1 as potential stimulation site for LIDs treatment. First, Filipovic et al. [7], using low-frequency rTMS (1 Hz) for 4 consecutive days in ten PD patients with LIDs, reported residual beneficial clinical effects in dyskinesia severity. With the same TMS protocol, these authors found an increased beneficial effect also in one PD patient with diphasic dyskinesia [8]. Finally, in another case report, rTMS over the M1 significantly reduced the painful dystonia and walking disturbances in one dyskinetic patient with painful off-period dystonia [9].

Despite these conflicting findings, a central role of M1 in the genesis of LIDs may be hypothesized since it has been

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demonstrated the presence of D1 and D2 receptors in motor cortex together with the fact that M1 plasticity was defective in advanced PD patients [13]. Since till now the "direct" M1 modulation by NIBS has shown no clear and reproducible clinical benefits, an alternative and feasible strategy to restore this defective plasticity should be attempted, i.e., exciting or inhibiting distant M1-related interconnected brain areas. The recent functional and structural neuroimaging results published in the last 5 years have offered neurophysiological basis to this strategy suggesting that LIDs-related symptoms may originate in brain network beyond the "classical" basal ganglia dysfunctional model, including cortical regions strongly involved in motor inhibition processes. Indeed, what has been clearly demonstrated was that the functionality of the IFC, SMA/pre-SMA as well as the cerebellum was impaired in PD patients with LIDs [10, 14–17]. These regions are parts of the well-known neural network involved in motor inhibition [18] or are directly involved in modulation of M1 excitability [17]. Following this later imaging evidence, our group demonstrated that [10] a single session of continuous but not intermittent or sham TBS applied over the right IFC was able to significantly reduce the amount of dyskinesias as measured by the conventional abnormal involuntary movement scale (AIMS). Koch's group was the first in using rTMS approach with therapeutical purpose. They demonstrated [11] that one single session of low frequency (1 Hz) rTMS over the SMA produced significant motor improvements (as indicated by AIMS scores) in eight LIDs patients. The rationale behind the choice to stimulate SMA is based on the notion that repeated sessions of premotor cortex stimulation induce cumulative changes leading to distant and persistent modifications in the excitability over the M1 [19]. With this in mind, Brusa et al. [12] tried to translate this single TMS protocol in a prolonged therapeutic session (5 days), failing to demonstrate a clear beneficial effect.

Otherwise, prolonged inhibitory NIBS therapeutic sessions applied as continuous theta burst stimulation (cTBS) over the cerebellar cortex yielded persistent clinical beneficial effects for up to 4 weeks after the end of the daily stimulation period [20]. To explain the greater effectiveness reached targeting the cerebellum rather than SMA [11], Koch et al. [20] claimed that the cerebellum is a subcortical structure directly involved in motor learning more than the SMA and therefore could be susceptible to more sustained rTMS-induced changes, leading to marked clinical beneficial effects. Furthermore, it was demonstrated that in healthy subjects the rTMS-induced cerebellar inhibition leads to an increase in sensorimotor plasticity [21] that, in its turn, is lacking in advanced PD patients [13]. For this reason, the evidence presented above together with those found by Ferrucci et al. [1] would seem to suggest that inhibiting cerebellum could be a strategy to restore defective sensorimotor plasticity in PD with LIDs.

To sum up, the current literature on therapeutic trials of brain stimulation in PD patients with LIDs is in its relative infancy. However, the search for the most effective protocol leads us to the conclusion that NIBS on cortical regions part of the motor inhibition network or on M1-related interconnected brain areas (i.e., cerebellum) might be highly promising as therapeutical sites for treatment of LIDs.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest.

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