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Applications of Repetitive Transcranial Magnetic Stimulation on Motor Symptoms in Parkinson's Disease

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Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a valuable non-invasive brain stimulation tool for interventional neurophysiology applications. It is used to modulate brain activity in specific, distributed, cortico-subcortical networks [1]. rTMS induces electric currents in the brain by producing a magnetic field perpendicular to the coil plane. This magnetic field is made to pass through the skull. The induced currents either activate neurons or induce synaptic plasticity by acting upon interneurons in the brain [2]. There are two main rTMS stimulation coil shapes namely the circular coil shape, which enables wide stimulation and the figure-of-8 coil shape, which permits focal stimulation. However, new coils that enable wide and deep stimulation are being developed [3,4], and it is becoming more common to select a coil based on the disease and site of stimulation. rTMS produces a sustained effect even after the end of the stimulation through repetitive application of stimuli with a specific rhythm. Stimulation parameters, mainly frequency, influence its modulatory effect in terms of resulting excitation or inhibition. High-frequency stimulation (often defined as being ≥ 5 Hz) has been shown to facilitate cortical excitability, whereas low-frequency stimulation (≤ 1 Hz) was shown to decrease or control cortical excitability. The most prevalent side-effects are discomfort and complaints of headache. These are mostly no serious adverse effects. Although seizures have been reported as a critical adverse effect, the current state of knowledge favors increasing stimulation frequency rather than intensity for reasons of safety defined according to the risk of seizures [5].

Parkinson's Disease

Parkinson's disease (PD), the second most common neurodegenerative disease, is a progressive debilitating neurodegenerative disease that affects dopaminergic neurotransmission, thereby resulting in motor and non-motor symptoms. Motor dysfunction in PD is mainly manifested as resting tremors, rigidity, bradykinesia and postural instability [6]. Various therapeutic approaches have been developed for the treatment of PD. Pascual-Leone et al. first reported improvement in upper extremity movements in PD patients who had received rTMS. Many studies concerning the use of rTMS in PD have focused on its beneficial effects on motor function. A study involving meta-analyses found modest efficacy of high-frequency rTMS on motor function in PD [7,8]. rTMS also has the potential to be used for clinical therapy, as several available studies involving PD patients have shown.

Area for Stimulation

The systematic review [9] demonstrated the therapeutic effects of rTMS on motor symptoms in PD, as evaluated with the motor section of the Unified Parkinson's Disease Rating Scale part III (UPDRS-III). However, the best area of the brain for stimulation remains unknown, various cortical targets, including the primary motor cortex (M1), supplementary motor area (SMA), and left dorsolateral prefrontal cortex (DLPFC), has been reported. After application of high-frequency (HF)-rTMS over the M1, most studies have demonstrated that PD patient's exhibit improved motor function in their hands and gait [10-12]. The HF-rTMS over the M1 suggested being increased motor-related activity in the caudate nucleus. Even so, other studies have reported no beneficial effects of this stimulation [13]. In one study, an rTMS of 5 Hz over the SMA modestly improved motor symptoms in patients with PD [14]. Another study, which aimed to improve disturbance in mood in PD patients by applying rTMS over the DLPFC, demonstrated positive effects on depression level [15]. Moreover, a few other studies have reported positive effects and improvement in motor symptoms in PD patients who received rTMS over the DLPFC [16]. Therefore, optimal parameters for rTMS remain to be established. To address this issue, we sought to identify the best cortical area for HF-rTMS therapy in patients with PD by conducting a double-blind, placebo-controlled, crossover study. After application of HF-rTMS over the M1, SMA, DLPFC and sham, we compared the results to those obtained during sham stimulations [17]. This study reported that the UPDRS-III scores following the application of HF-rTMS over the M1 and SMA was significantly greater than that following sham stimulation. In contrast, changes in UPDRS-III scores following bilateral rTMS over the DLPFC were not different from those after sham stimulation. No significant changes emerged for either the depression or apathy scores following HF-rTMS over any cortical area. Therefore, application of HF-rTMS over the M1 and SMA significantly improved the motor symptoms in patients with PD but did not improve mood disturbances. Many positive studies report improvement of bradykinesia, but diverge in their efficacy to treat other cardinal symptoms of PD. rTMS improved gait in several [18,19], but not all studies [20]. A few studies have reported finding improvement in tremor symptoms in PD patients who received rTMS. At present, the mechanisms of rTMS in relation to disturbances in motor function and mood in PD remain unclear and thus controversial. A hypoactive caudate nucleus may underlie the motor deficits in PD patients by interfering with the normal functioning of the striato-frontal motor loop. Applying HF-rTMS over the M1 may partially compensate for the underactive basal ganglia-thalamocortical outflow to the frontal motor cortical areas

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and induce lasting enhancement in cortical excitability, thus leading to clinical improvement. Strafella et al. [21] showed that applying rTMS over the M1 increased dopamine release in the nigrostriatal system. On the other hand, SMA is suggested be important in motor planning and preparatory processes in PD [22]. The studies using positron emission computerized tomography for cortical activation in PD patients with akinesia-predominant Parkinsonism suggested the involvement of hypoactive SMA and dorsal premotor areas [23]. Decreased activity in the SMA was considered to be due to less efferent feedback from the basal ganglia-thalamocortical motor loop A randomized clinical trial reported that HF-rTMS (5 Hz) over the SMA could modestly ameliorate motor symptoms in patients with PD [17]. However, in a subsequent study, the same authors reported long-lasting therapeutic benefits of LF-rTMS (1 Hz) over the SMA, but not of HF-rTMS (10 Hz) over the same area or the realistic sham stimulation [24]. Moreover, a recent subgroup analysis in a meta-analysis study demonstrated that HF-rTMS over the M1 and LF-rTMS over other frontal regions, including the SMA, could have a positive effect [25]. Yokoe et al. [17] demonstrated the positive effect of HF-rTMS over the M1 and SMA on motor symptoms in patients with PD [17]. However, there are some limitations of a crossover design, which include carry-over effects and order effects. Unlike single session rTMS, multi-session cumulative rTMS might provide a long-lasting effect in cortical excitability and function [26,27]. The postsynaptic changes and expansion of plasticity might underlie the cumulative long-lasting effect of rTMS [19].

Summary

The rationale for non-invasive brain stimulation in clinical practice is to provide additional benefit beyond conventional therapy. Future studies need to explore stimulation parameters with regards to efficacy and safety. In addition, these studies need to identify neurophysiological correlates of clinical outcome measures which will allow for the determination of superior stimulation patterns and therapeutic strategies for the improvement of PD and other disorders.

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