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The optimal stimulation site for high-frequency repetitive transcranial magnetic stimulation in Parkinson's disease: A double-blind crossover pilot study

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ABSTRACT

Many reports have shown improvements in motor symptoms after repetitive transcranial magnetic stimulation (rTMS). However, the best stimulation area in the brain has not currently been determined. We assessed the effects of high-frequency rTMS (HF-rTMS) on the motor and mood disturbances in Parkinson's disease (PD) patients and attempted to determine whether the primary motor area (M1), the supplementary motor area (SMA), and the dorsolateral prefrontal cortex (DLPFC) were the best treatment targets. In this randomized, double-blind crossover design study, we investigated the efficacy of 3 consecutive days of HF-rTMS over the M1, SMA, and DLPFC and compared these HF-rTMS to sham stimulations. We used motor and non-motor scales to evaluate the parkinsonian symptoms. The changes in the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) scores after the application of HF-rTMS over the M1 and SMA were significantly greater than those after the sham stimulation. However, after the application of HF-rTMS over the DLPFC, the UPDRS-III scores were similar to those after the sham stimulation. No significant improvements were demonstrated in the mood disturbances after the stimulations over any of the targets. In conclusion, the application of HF-rTMS over the M1 and SMA significantly improved the motor symptoms in the PD patients but did not alter the mood disturbances.

1. Introduction

Parkinson's disease (PD) is a progressive, debilitating neurodegenerative disease that affects dopaminergic neurotransmission, thereby resulting in motor and non-motor symptoms. The non-motor symptoms are the most common symptoms in PD patients and progress throughout the course of the disease. Although the non-motor symptoms deteriorate the patients' quality of life, treatments for PD primarily focus on improving the motor symptoms. Repetitive transcranial magnetic stimulation (rTMS) is an emerging adjunctive therapeutic modality that is used to treat movement disorders. rTMS is a non-invasive technique in which the cerebral cortex is repeatedly stimulated by a train of magnetic pulses. Pascual-Leone et al. first reported improvements in the upper extremity movements of PD patients who had received rTMS [1]. Thus, many subsequent clinical trials have examined the use of rTMS in PD and reported that rTMS was clinically effective in the treatment of the motor symptoms in PD patients [2–9].

Many studies have demonstrated that PD patients exhibit an ameliorated motor function in the hand and even gait after the application of high-frequency (HF)-rTMS over the primary motor area (M1) [4,7]. There are also a number of state-of-the-art ran-

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; PD, Parkinson's disease; M1, primary motor cortex; SMA, supplementary motor area; DLPFC, dorsolateral prefrontal cortex; VAS, visual analogue scale; AES, the Apathy Evaluation Scale; MADRS-S, the Self-Rated the Montgomery Åsberg Depression Rating Scale version; SDS, the Self-Rating Depression Scale; STN, the subthalamic nucleus.

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domized controlled trials that have reported negative results [10–14]. Both positive and negative results have been reported regarding the application of HF-rTMS over the supplementary motor area (SMA); thus, the efficacy of HF-rTMS over the SMA remains inconclusive [15,16]. Another study attempted to improve the mood disturbances in PD patients, and after the application of rTMS over the left dorsolateral prefrontal cortex (DLPFC), the results demonstrated positive effects in terms of the patients' depression level [17]. However, many studies have reported that there were no beneficial effects associated with this treatment. Moreover, a few other studies have reported positive effects and improvements in the motor symptoms in PD patients after the application of rTMS over the DLPFC [17–19]. Although mood disturbances are responsible for a large number of PD impairments, the main focus of PD treatments is the improvement of the motor symptoms. A meta-analysis has demonstrated that rTMS improves motor symptoms in PD patients, and a subgroup analysis has shown that HF-rTMS over the M1 and low-frequency (LF) rTMS over other frontal regions significantly improved the motor symptoms, but the HF-rTMS appears to be better [20,21]. However, to date, meta-analyses that examine the effects of rTMS on mood disturbances in PD patients have not been conducted.

In the most recent study, rTMS over the M1 was an effective treatment for the motor symptoms, but rTMS over the DLPFC did not show a mood benefit [9]. HF-rTMS over the SMA has also been suggested to modestly improve the motor symptoms in patients with PD [15]; however, no studies have compared the application of HF-rTMS over the M1 to that over the SMA. Each of the previous rTMS studies examined different parameters (e.g., coil type, stimulus locations, frequency, intensity, and sham stimulation). These considerable methodological differences across studies, such as the rTMS parameters and the evaluation methods, appear to be simple explanations for the controversial results. These results indicate a noteworthy lack of consensus regarding the specifications of the optimal stimulation area for PD treatment. Therefore, we sought to determine which cortical area is the most promising target for HF-rTMS therapy in patients with PD by conducting a double-blind, placebo-controlled, crossover study. The aim of this exploratory study is to identify an appropriate outcome measure for subsequent studies.

2. Material and methods

2.1. Trial design

This randomized, double-blind, placebo-controlled crossover study examined the effect of a bilateral stimulation over the M1, SMA, or DLPFC compared with that observed after a sham stimulation. At each location, the rTMS was repeated for 3 consecutive days. To minimize any carryover effects between the different locations, the subjects underwent an interval of 4 or more days prior to any subsequent stimulation. Fig. 1 shows the timeline of the rTMS protocol. The independent statistician generated the random allocation sequence by the independent statistician generated the random allocation sequence. Patients continued to take their medications during the study period to evaluate the additive effect of the rTMS. All rTMS sessions were performed at the same time of day throughout the daily treatment cycle. At the start of the study, all patients had been taking a fixed dose of their usual anti-PD medication for at least 2 weeks. Both the patients and the assessors were blinded to the group assignments until after the study was completed.

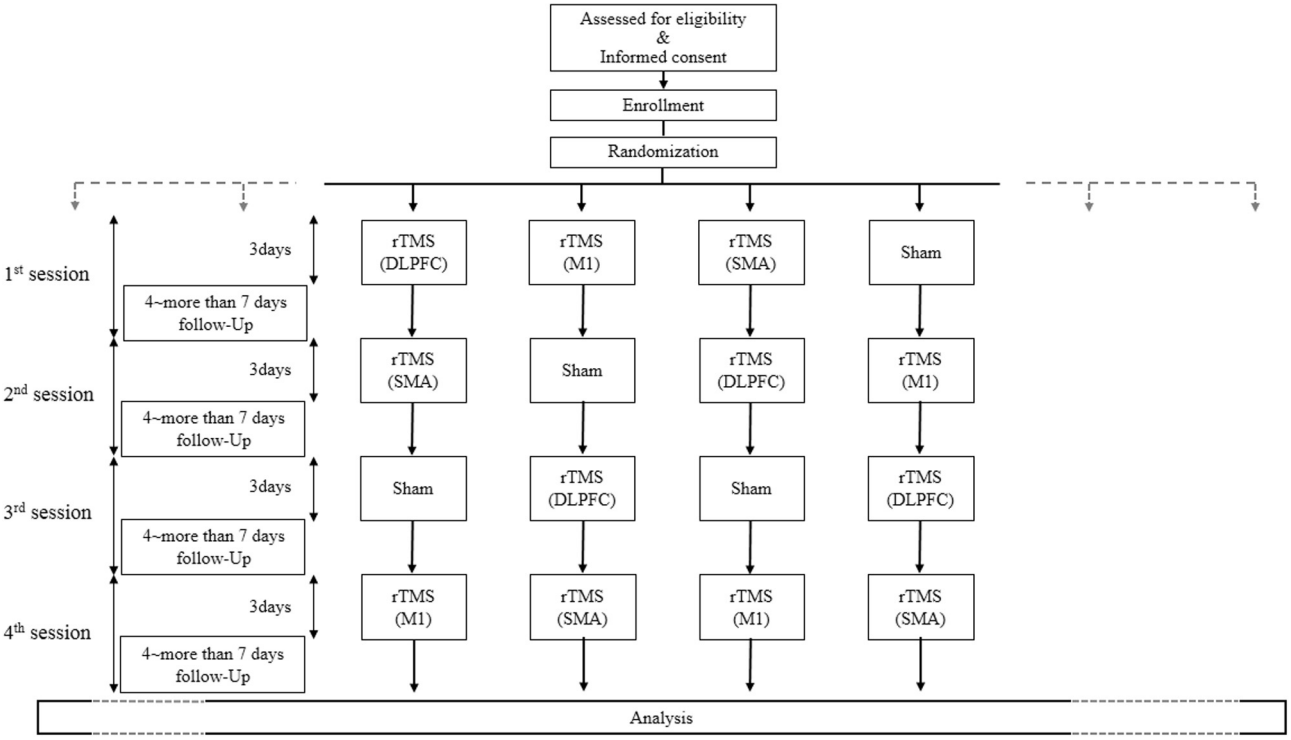

Fig. 1. Study design. This study used a placebo-controlled, crossover design. The treatments performed in all PD patients included rTMS over the M1, SMA, DLPFC and sham stimulation (placebo). All treatments were performed daily over a period of three days each. The order of the rTMS treatments was randomly assigned. The patients and assessors were blinded to the group assignments until after the completion of the study. To evaluate the effect of each rTMS session, all examinations were performed immediately before and approximately 1 h after each rTMS session. Over the three days during which the patients were assessed, all evaluations were conducted at the same time after the patients had received their medication and before their next medication requirement.

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