Repetitive transcranial magnetic stimulation for Parkinson's disease

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neuromodulation technique that has been closely examined as possible Parkinson's disease treatment.

Cortical Electrostimulation (CES) can modulate cortical excitability through a plasticity-like mechanism and is considered to have potential in Parkinson's disease treatment (PD). However, the precise therapeutic value of such an approach for PD remains unclear. Accordingly, Kuo et al. adopted a PD rat model to determine the therapeutic effects of CES. The current study was thus designed to identify the therapeutic potential of CES in PD rats.

A hemiparkinsonian rat model, in which lesions were induced using a unilateral injection of 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle, was applied to identify the therapeutic effects of long-term (4-week) CES with intermittent theta-burst stimulation (iTBS) protocol (starting 24 h after PD lesion observation, 1 session/day, 5 days/week) on motor function and neuroprotection. After the CES intervention, detailed functional behavioral tests including gait analysis, akinesia, open-field locomotor activity, apomorphine-induced rotation as well as degeneration level of dopaminergic neurons were performed weekly up to postlesion week 4.

After the CES treatment, they found that the 4-week CES intervention ameliorated the motor deficits in gait pattern, akinesia, locomotor activity, and apomorphine-induced rotation. Immunohistochemistry and tyrosine hydroxylase staining analysis demonstrated that the number of dopamine neurons was significantly greater in the CES intervention group than in the sham treatment group.

This study suggests that early and long-term CES intervention could reduce the aggravation of motor dysfunction and exert neuroprotective effects in a rat model of PD. Further, this preclinical model of CES may increase the scope for the potential use of CES and serve as a link between animal and PD human studies to further identify the therapeutic mechanism of CES for PD or other neurological disorders [1].

Data were acquired during resting state on 34 Parkinson's disease patients and 25 controls. The ratio of standard uptake value for PET images and the subthalamic nucleus (STN) Dynamic functional connectivity (FC) maps for fMRI data were generated. The metabolic connectivity mapping (MCM) approach that combines PET and fMRI data was used to evaluate the direction of the connectivity. Results showed that PD patients exhibited both increased FDG uptake and STN-FC in the sensorimotor area ($P_{FDR} < 0.05$). MCM analysis showed higher cortical-STN MCM value in the PD group ($F = 6.63$, $P = 0.013$) in the left precentral gyrus. There was a high spatial overlap between the increased glucose metabolism and increased STN-FC in the sensorimotor area in PD. The MCM approach further revealed an exaggerated cortical input to the STN in PD, supporting the precentral gyrus as a target for treatment such as the repetitive transcranial magnetic stimulation [2].

40 Parkinson's disease patients with freezing of gait, 31 without freezing of gait, and 30 normal controls. A subset of 30 patients with freezing of gait (verum group: N = 20; sham group: N = 10) who participated the aforementioned rTMS study underwent another scan after the treatments. Using the baseline scans, the imaging biomarkers for freezing of gait and Parkinson's disease were developed by contrasting the connectivity profiles of patients with freezing of gait to those without freezing of gait and normal controls, respectively. These two biomarkers were then interrogated to assess the rTMS effects on connectivity patterns. Results showed that the freezing of gait biomarker was negatively correlated with Freezing of Gait Questionnaire score ($r = -0.6723$, $p < 0.0001$); while the Parkinson's disease biomarker was negatively correlated with MDS-UPDRS motor score ($r = -0.7281$, $p < 0.0001$). After the rTMS treatment, both the freezing of gait biomarker (0.326 ± 0.125 vs. 0.486 ± 0.193, $p = 0.0071$) and Parkinson's disease biomarker (0.313 ± 0.126 vs. 0.379 ± 0.155, $p = 0.0378$) were significantly improved in the verum group; whereas no significant biomarker changes were found in the sham group. The findings indicate that high-frequency rTMS over the supplementary motor area confers the beneficial effect jointly through normalizing abnormal brain functional connectivity patterns specifically associated with freezing of gait, in addition to normalizing overall disrupted connectivity patterns seen in Parkinson's disease [3)].

In 2017 a study aimed to review the effectiveness of repetitive transcranial magnetic stimulation (rTMS) for Parkinson's disease (PD). Randomized, double-blind, sham-controlled, multicenter studies on rTMS for PD have been conducted three times in Japan (in 2003, 2008, and 2013). These studies revealed that 5-Hz rTMS over the supplementary motor area (SMA) is the most effective modality for improving motor symptoms. Several functional imaging studies showed reduced SMA excitability in patients with PD, probably secondary to basal ganglia dysfunction. Therefore, 5-Hz rTMS is assumed to normalize SMA excitability and amend basal ganglia function secondarily. Currently, a phase III trial is being conducted in Japan. Therefore, in the near future, 5-Hz rTMS can be used as a therapeutic modality for PD treatment. In addition, several powerful rTMS have been developed recently, including quadripulse stimulation (QPS), which most potently induces neural plasticity. QPS is also expected to be a potential therapeutic tool to treat patients with PD [4)].

In 2015 Twenty studies with a total of 470 patients were included. Random-effects analysis revealed a pooled SMD of 0.46 (95% CI, 0.29-0.64), indicating an overall medium effect size favoring active rTMS over sham rTMS in the reduction of motor symptoms (P<.001). Subgroup analysis showed that the effect sizes estimated from high-frequency rTMS targeting the primary motor cortex (SMD, 0.77; 95% CI, 0.46-1.08; P<.001) and low-frequency rTMS applied over other frontal regions (SMD, 0.50; 95% CI, 0.13-0.87; P=.008) were significant. The effect sizes obtained from the other 2 combinations of rTMS frequency and rTMS site (ie, high-frequency rTMS at other frontal regions: SMD, 0.23; 95% CI, -0.02 to 0.48, and low primary motor cortex: SMD, 0.28; 95% CI, -0.23 to 0.78) were not significant. Meta-regression revealed that a greater number of pulses per session or across sessions is associated with larger rTMS effects. Using the Grading of Recommendations, Assessment, Development, and Evaluation criteria, we characterized the quality of evidence presented in this meta-analysis as moderate quality.

The pooled evidence suggests that rTMS improves motor symptoms for patients with PD. Combinations of rTMS site and frequency as well as the number of rTMS pulses are key modulators of

rTMS effects. The findings of our meta-analysis may guide treatment decisions and inform future research [5].

Randomized, double-blind, sham-controlled, multicenter studies on rTMS for PD have been conducted three times in Japan (in 2003, 2008, and 2013). These studies revealed that 5-Hz rTMS over the supplementary motor area (SMA) is the most effective modality for improving motor symptoms. Several functional imaging studies showed reduced SMA excitability in patients with PD, probably secondary to basal ganglia dysfunction. Therefore, 5-Hz rTMS is assumed to normalize SMA excitability and amend basal ganglia function secondarily. Currently, a phase III trial is being conducted in Japan. Therefore, in the near future, 5-Hz rTMS can be used as a therapeutic modality for PD treatment. In addition, several powerful rTMS have been developed recently, including quadripulse stimulation (QPS), which most potently induces Neuroplasticity. QPS is also expected to be a potential therapeutic tool to treat patients with PD [6].

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52 Parkinson's disease (PD) patients were randomly classified into two groups. The first group received 20 Hz and the 2nd group received 1 Hz Repetitive Transcranial Magnetic Stimulation (rTMS) with a total of 2000 pulses over M1of each hemisphere for ten days. Effects were assessed with the Unified Parkinson's Disease Rating Scale part III (UPDRS), Instrumental Activity of Daily Living (IADL), and a self-assessment score (SA) before, after the last session, and one month later. Cortical excitability was measured before and after the end of sessions.

There was a significant improvement on all rating scales after either 1 Hz or 20 Hz rTMS, but the effect persisted for longer after 20 Hz (treatment X time interaction for UPDRS and IADL (P = 0.075 and 0.04, respectively). Neither treatment affected motor thresholds, but 20 Hz rTMS increased MEP amplitude and the duration of transcallosal inhibition. In an exploratory analysis, each group was subdivided into akinetic-rigid and tremor dominant subgroups and the effects of 1 Hz and 20 Hz treatment recalculated. There was weak evidence that patients with an akinetic-rigid presentation may respond better than those with predominant tremor.

Both 20 Hz and 1 Hz rTMS improve motor function in PD, but 20 Hz rTMS is more effective [7].

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