Effect of Repetitive Transcranial Magnetic Stimulation on fMRI Resting-State Connectivity in Multiple System Atrophy

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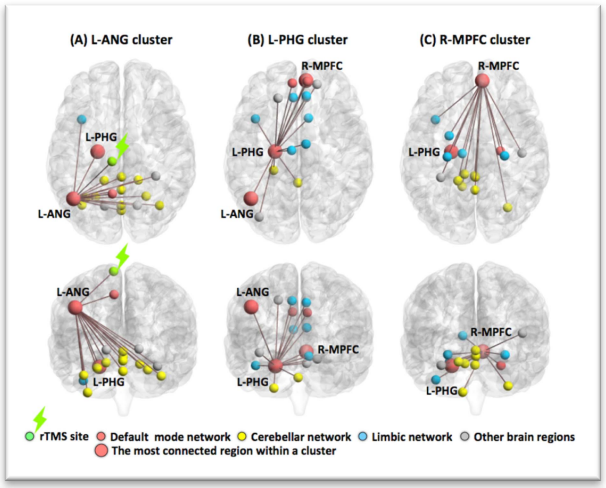
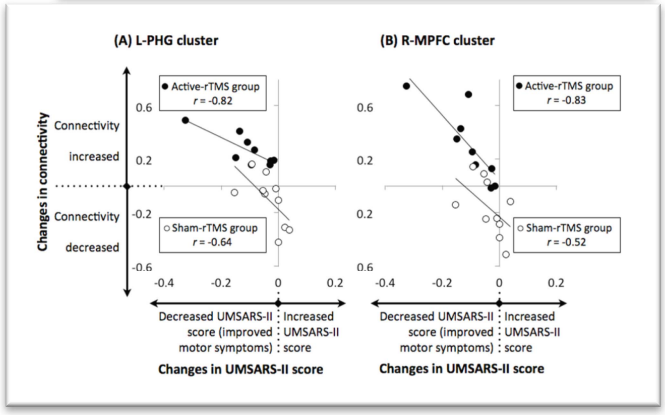
Target Audience: Researchers and clinicians interested in repetitive transcranial magnetic stimulation (rTMS) and brain functional connectivity

Purpose: rTMS is a non-invasive neuromodulation technique that has been used to treat neurological and psychiatric conditions. Although results of rTMS intervention are promising, so far little is known about the rTMS effect on brain functional networks in clinical populations. In this study we investigated the relationship between rTMS intervention, resting-state functional connectivity, and motor symptoms in patients with multiple system atrophy (MSA). MSA is an adult-onset, sporadic, progressive neurodegenerative disease characterized by a combination of symptoms that affect both autonomic nervous system and movement [1]. Some of the motor symptoms, such as bradykinesia, rigidity, gait instability and tremor, are similar to those of Parkinson's disease (PD) [2]. However, patients with MSA usually respond poorly to dopamine replacement therapy [1]. Given the limited efficacy of pharmacological treatment in improving motor symptoms of MSA [1], there is a clinical need to determine whether and how rTMS could benefit this population.

Methods: This randomized, double-blind, sham-rTMS controlled trial included 19 patients who were diagnosed as having probable MSA with predominant parkinsonism according to the established consensus criteria. Patients were randomized to active-rTMS or sham-rTMS group and completed a 10-session 5Hz rTMS treatment over 2 weeks. The rTMS was performed over the left primary motor area (M1). The motor score of the Unified Multiple System Atrophy Rating Scale (UMSARS-II) and resting-state fMRI were measured before and after the 10-session rTMS treatment. For each participant, the preprocessed resting-state fMRI data were parceled into a set pf 116 brain regions (90 within the cerebral cortex and 26 within he cerebellum) using the Automated Anatomical Labeling template [AAL, 3]. We used Pearson correlation as the metric of association between the time series for each pair of the 116 brain regions. This resulted in a 116 x 116 correlation matrix with 6670 ([116 x 115]/2) unique inter-regional correlation coefficients (r). These inter-regional r values were transformed to Zr values with Fisher's r-to-z transformation [4].



Results: All patients tolerated rTMS well without adverse effects. The results of two-way ANOVA with rTMS (active-rTMS vs. sham-rTMS) as an independent factor and time (pre-rTMS vs. post-rTMS) as a repeated factor showed significant rTMS-related changes in motor symptoms and functional connectivity. Specifically, 1) significant improvement of motor symptoms was observed in the active-rTMS group, but not in the sham-rTMS group; and 2) several functional links involving the default mode network (DMN) exhibited significantly greater increment in functional connectivity in the active-rTMS group relative to the sham-rTMS group (Fig 1). Multiple comparisons were corrected at $p < 0.05$ based on data distribution patterns determined by 10,000 Monte Carlo simulations. Moreover, the increased functional connectivity was associated with improvement in motor symptoms for the active-rTMS group (Fig. 2).



Discussion & Conclusion: All the ANOVA-identified functional links, corrected for multiple comparisons, were connected to brain regions (i.e., right medial prefrontal cortex, left parahippocampal gyrus, and left angular gyrus) that are typically categorized within the DMN. This result is consistent with a number of recent findings applying non-invasive brain stimulations (e.g., rTMS, transcranial direct current stimulation, or theta burst stimulation) to healthy adults [5-7] and patients with depression [8]. Relative to other brain regions, the DMN shows disproportionately high glucose metabolism [9] and regional blood flow during rest [10], and is considered to be involved in a high degree of neuroplasticity [11]. Although the mechanisms underlying modulations of the DMN are not yet clear, it seems plausible that the DMN plasticity might be sensitive to the rTMS treatment effects and the consolidation and maintenance of brain function might be facilitated via the DMN plasticity. The present findings suggest that rTMS may improve motor symptoms by modulating DMN-related functional connectivity, inferring a future therapeutic candidate for patients with MSA.

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