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Supplementary Material

Article Title: Frontostriatal Connectivity Changes in Major Depression After Repetitive Transcranial Magnetic Stimulation: A Randomized Sham-Controlled Study

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List of Supplementary Material for the article

1. **eAppendix 1** Supplementary Method

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eAppendix 1. Supplementary Method

fMRI procedures and data analyses

Functional MRI data were acquired using a 1.5 T MR scanner (Sigma Eclipse, GE Medical Systems, Waukesha, WI, USA). Scans were performed on the same day as the clinical and neurocognitive assessments. Subjects were instructed to remain still during the scan with their eyes fixed on the crosshairs of a slide with a black background. The participants' heads were cushioned with attached earmuffs. Thirty contiguous 5-mm-thick axial slices covering the entire brain were collected using the T2-weighted echo planar imaging sequence depicting the blood-oxygenation-level-dependent (BOLD) signal (TE = 22 ms; TR = 2000 ms; flip angle = 90°; field of view = 240 mm; 5-mm slice thickness; a matrix, 64 × 64 × 30; and spatial resolution, 3.75 × 3.75 × 5). Next, high-resolutionT1-weighted fast spoiled gradient echo sequence MR images (116 coronal slices with 1.5-mm slice thickness; TE = 18 ms; TR = 85 ms; flip angle = 12°; field of view = 240 mm; a matrix, 256 × 256 × 116; and spatial resolution, 0.94 × 0.94 × 1.5) were collected.

Preprocessing and statistical analyses of the fMRI data were performed using the Analysis of Functional NeuroImages (AFNI, http://afni.nimh.nih.gov/, Ver. 2011_05_26_1457) [1] software. The first 14 volumes were discarded to allow for the BOLD signal equilibration. Corrections for the differences in slice acquisition time and head movements were performed for all slices within a volume. Corrected images were normalized to the standard 152 T1 template of the Montreal Neurological Institute (MNI) space provided by AFNI, using the parameters from spatial normalization of T1-weighted images. All voxels were resampled as 2 × 2 × 2 mm size by linear

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interpolation. Normalized images were smoothed with a 6-mm full-width at half-maximum Gaussian filter. A temporal band-pass filtering was applied at 0.01 Hz < f < 0.08 Hz. [2, 3] The time courses representing large ventricle, white matter and global signal were regressed out during analyses to reduce the confound effects related physiological processes. The six head motion parameters and the zero-order through fourth-order trends in the BOLD time series were also regressed out.

For the purposes of ROI placement for sampling in functional connectivity analyses, we used the seed ROI of bilateral DLPFC, which was defined as a 20mm radius sphere (centered at x, y, z coordinates ± 41, 16, 54). Reference time series were obtained by averaging the fMRI time series within the DLPFC ROIs. Individual functional connectivity maps were produced by computing the correlation coefficient between the average BOLD time course extracted from the seed regions and the time courses from all other brain voxels. In order to avoid extraneous contribution by probable large ventricle voxels, we excluded voxels in the large ventricle from the functional connectivity maps using the large ventricle mask. The functional connectivity strengths were generated by converting the correlation coefficients to z values as a normal distribution using Fisher's z transformation. Next, we obtained the individual contrast maps that demonstrated changes in the functional connectivity strength between before and after rTMS sessions (i.e., pre-TMS minus post-TMS). To examine group differences, we performed two-sample t-tests on contrast maps between the active and the sham groups. Statistically-defined clusters of activation were identified using the whole-brain Monte Carlo simulations (Alpha-Sim program by AFNI) to achieve a corrected cluster threshold of p < 0.05. Specifically, clusters reaching a contiguous volume of at least 296 mm^3 at a voxel-wise threshold of p < 0.001 were considered significant at corrected p <0.05. In order to refine a location of clusters, we constructed a study-specific anatomical template by averaging spatial normalized T1-weighted image across all participants.

In addition, the individual connectivity strength values before (pre-TMS) and after the 2-week rTMS (post-TMS) were extracted by averaging across all voxels based on the survived clusters

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in group analyses. To assess the potential influence of subject outliers on the group difference, we conducted a two-sample t-test using a (n - 1) jackknife approach for the reduction degree values of functional connectivity. In the post hoc analysis, to examine hemispheric effect of the seed ROI to results of the group difference of the functional connectivity, we obtained the reduction degree values of functional connectivity derived from each left and right DLPFC seed region in the clusters from the between-group differences. We performed a repeated measure analysis of variance with factors of seed hemisphere and two groups using these values.

For the statistical analyses of clinical and demographic data, we used t-tests on continuous variables and Fisher's exact tests on categorical variables to evaluate between-group differences. To examine if there was an effect of group or time for the outcome measures of HAMD and neurocognitive tasks, repeated measure analyses of variance were performed. In addition, Spearman's correlation analyses were conducted to explore how functional connectivity changes were related to the depression severity or neurocognitive function and were further tested using a jackknife approach and a bootstrap procedure with replacement in 10000 samples to obtain the estimates of statistical accuracy of correlation coefficients. Statistical analyses were performed using the SPSS v.21.0 (SPSS, Chicago, IL, USA). All tests were two-tailed, and significance was accepted at $p < 0.05$.

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