The Duration and Extent of effects of Neuronavigated Low-Frequency rTMS to Primary Motor Cortex using fMRI in Healthy Subjects

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Introduction

Neuronavigated low-frequency repetitive transcranial magnetic stimulation (rTMS) is known to produce local and interhemisperic neuromodulatory effects on cortical excitability with accuracy in targeting of a given cortical region. However there have been few studies about the duration and extent of neuromodulatory effect in neuronavigated rTMS using functional magnetic resonance image (fMRI). Therefore, in this study, we investigated the extent and duration of neuromodulatory effect of rTMS with fMRI. Furthermore, we hypothesized that the effect of rTMS at motor cortex can possibly modulate not only interhemisperic motor behavior but also non-motor related brain regions.

Subjects and Methods

Twenty healthy subjects (14 male, 6 female, mean age 28.55±3.07) underwent two experimental sessions during they received 600 pulses of either real or sham 1Hz rTMS at 90% of the resting motor threshold (RMT) intensity over the left primary motor cortex. We compared the effects of real and sham stimulation through post stimulation three consecutive fMRI acquisitions during performing right finger tapping task (pre, post 1, post 2, post 3, Fig. 1). The MRI examinations were performed with 3.0 Tesla whole body scanner (Signa Exite HD, GE, USA) with a 8 channel head coil. (EPI, TR=3000ms, TE =30ms, flip angle =90 , matrix=64x64, FOV=210mm, slice thickness = 4 mm, no gap). A 3-D T1-weighted scan was obtained for structural reference. Image processing and statistical analyses were performed using MATLAB (The Math works Inc., Natick, MA, USA) and SPM8 (SPM;Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk). The pre-processed fMRI data were entered into first-level individual analysis in order to obtain parameter images for the contrasts of each condition. Second-level group analysis with one-way ANOVA (within subject) was then used to find the main effect of between contrast differences. The SPM{F}s were thresholded at P<0.05, false discovery rate (FDR)-corrected for multiple comparisons across the whole brain. In addition, post-hoc two sample t-test was performed for determination of difference between two conditions. The SPM{t}s were thresholded at P<0.05, using a Bonferroni adjusted alpha level of 0.0084, FDR-corrected for multiple comparisons across the whole brain. The result of the activation map was displayed by projection of an anatomically standardized mean T1 template. All subjects signed an informed consent and agreed to participate in the fMRI study. The study protocol was approved by the Institutional Review Board.

Results and Discussion

The within group analysis using one sample t-test of right finger tapping task before rTMS stimulation revealed the activation at the left primary motor cortex and SMA (Fig. 2a), After rTMS stimulation at the left primary motor cortex, the within group analysis of right finger tapping task showed that the activities of ipsilateral motor network (left primary motor cortex and left SMA) were reduced at post1 and post2, and the activities at the contralateral motor areas (right primary motor cortex and right SMA) and at the non-motor areas associated with attention, visuospatial, executive functions were gradually increase (Fig 2b, c). At post3, the activities of ipsilateral motor network were recovered and the activities at the contralateral motor areas and at the non-motor areas were decreased (Fig 2d). One-way ANOVA analysis for four conditions showed neural activation in the primary motor cortex, supplementary motor area, insula, inferior frontal gyrus, and cingulate gyrus (Fig 3). Post-hoc two sample t-test was performed for further comparison between conditions. Post-hoc two sample analysis revealed that stimulated (ipsilateral) motor cortex showed decreased activation at post 2 compared to pre-stimulation (Fig 4). However, rTMS lead to increased activity at the contralateral motor network and at the insula, inferior frontal gyrus, and cingulate gyrus, which plays an important role in cognition such as executive function (Fig 5). Sham rTMS did not show any significant changes in motor or non-motor network in ANOVA analysis. In summary, navigated rTMS on primary motor cortex lead to robust modulation not only at the ipsilateral motor network, but also at the contralateral (unstimulated) hemisphere for more than 20 minutes. Our findings highlight the duration and extent of interhemispheric neuromodulation effects of rTMS with serial consecutive fMRI for the first time.

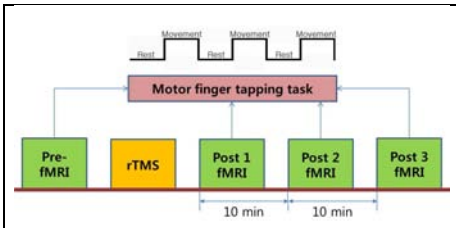

Figure 1. Experimental design

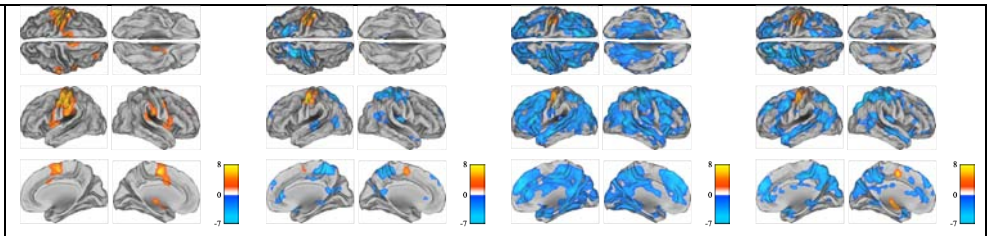

Figure 2. One sample t-test result (active area: Motor > rest, deactive area: rest > motor). The SPM{t}s were thresholded at P<0.05, FDR-corrected for multiple comparisons. (a) pre-rTMS, (b) post 1, (c) post 2, (d) post 3

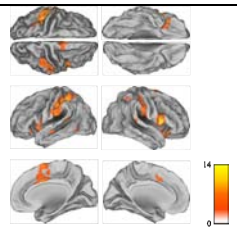

Figure 3. One-way within subject ANOVA with the 4 condition.(pre, post 1, post 2, post 3) The SPM{F}s were thresholded at P<0.05, false discovery rate (FDR)-corrected for multiple comparisons.

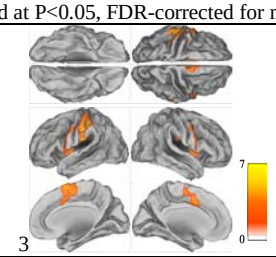

Figure 4. Post-hoc two sample t-test in active area (pre > post 2) The SPM{t}s were thresholded at P<0.05, using a Bonferroni adjusted alpha level of 0.0084, FDR-corrected for multiple comparisons.

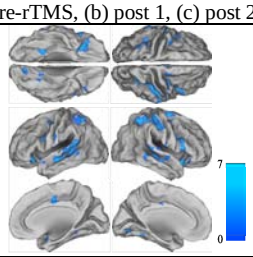

Figure 5. Post-hoc two sample t-test in deactive area. (post 2 > pre) The SPM{t}s were thresholded at P<0.05, using a Bonferroni adjusted alpha level of 0.0084, FDR-corrected for multiple comparisons.