Resting Connectivity Elucidates the Effect of Daily Priming Stimulation on the Motor Cortex

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INTRODUCTION Repetitive transcranial magnetic stimulation (rTMS) at low-frequency (1 Hz) can lead to inhibition of local cortical excitability resulting in a behavioral change that outlasts the stimulation [1]. The lasting inhibitory effect on neurons as a result of rTMS could potentially be utilized in treatment intervention for various neurological disorders [2]. Past work has demonstrated that priming stimulation at a higher frequency (6 Hz) before low-frequency stimulation can enhance cortical inhibition [3]. While immediate effects of rTMS have been extensively studied, there is little evidence on the long-lasting effects of low-frequency rTMS. Results from the same dataset indicate that low-frequency (1 Hz) rTMS with or without a 6 Hz priming stimulus can reduce local stimulus-induced hemodynamics but cannot distinguish the low-frequency rTMS with and without priming [4]. The present study examines the effect of 6 Hz priming followed immediately by 1 Hz rTMS to the primary motor area (M1) on resting connectivity after 5 consecutive days. To the best of our knowledge no studies have explored the effects of 1 Hz rTMS using resting state connectivity methods demonstrated in this study. We hypothesize that low-frequency rTMS would a) be more effective at depressing motor cortex excitability after priming with 6 Hz rTMS than after no priming and sham stimulation, b) cause depressive effects manifested as an overall decrease in the connectivity in M1 (ipsilateral) and SMA during the resting state and c) globally reduce connectivity following five consecutive days of rTMS relative to baseline. Our goal is to better understand the mechanism of action of rTMS in the healthy human brain as a precursor to potential treatment of a variety of neuropsychiatric disorders.

METHODS

Subjects and rTMS: We conducted a double-blind study of primed and unprimed real versus sham rTMS in five right-handed healthy volunteers (2 primed, 2 unprimed, 1 sham). TMS was performed using MAGSTIM Standard Rapid Stimulation centered over the optimal scalp site to elicit response in the right first dorsal interosseous (FDI) muscle. The intersection of the coil was oriented perpendicular to the assumed central sulcus at a 45° angle away from the midline, inducing a tissue current in the posterior-to-anterior direction. Prior to each rTMS session, the site of motor stimulation was defined as the location where the motor threshold was lowest while evoking the largest response [5]. These positions were confirmed in all subjects by an image-guided frameless stereotaxy system (Brainsight, Rogue Research, Montreal, Canada) to localize the sites of TMS of the hand motor area. Resting motor threshold (RMT) was defined as the minimum TMS intensity required to elicit at least 5 out of 10 motor evoked potentials (MEP) when applied over the right hand motor area of the left hemisphere at the frequency of 1 Hz [6]. Following the establishment of RMT, we applied 10 minutes of 6 Hz priming rTMS at 90% RMT (3,600 pulses for subjects receiving primed rTMS) followed by 30 minutes of 1 Hz rTMS at 95% RMT (1,800 pulses for all subjects). The 40 minute rTMS protocol was performed each day for five consecutive days and motor performance was also assessed during a baseline session and the tenth day after the start of rTMS.

Image Acquisition: Prior to rTMS application, we acquired baseline BOLD resting connectivity scans on a 3T Siemens Trio scanner. An EPI pulse sequence was used to acquire 280 images, with ten 5 mm thick axial slices (for 2 primed rTMS subjects and sham subject) and five 5 mm thick axial slices (for 2 unprimed rTMS subjects) with an in-plane resolution of 3.44 mm x 3.44 mm. Pulse sequence parameters were TR/TE/FA/FOV of 750 ms/35 ms/50°/22 cm. Identical image acquisition protocol was repeated immediately following the fifth consecutive day of rTMS.

ANALYSIS Functional connectivity maps were formed by using a seed in the most significant active voxel in left brodmann area 4 as determined from the stimulus-induced BOLD scan (on the side of rTMS application and contralateral to finger movement) from the same scanning session. The timecourses of 4 neighboring voxels at this seed location formed the reference ROI. Resting data was low-pass filtered < 0.08 Hz to avoid aliasing of the respiration and cardiac harmonics into the frequency band of interest, while keeping the frequencies that contribute to functional connectivity [7]. This reference was then correlated with the low-pass filtered resting-state data to form functional connectivity correlation maps using a threshold of $r > 0.4$. Connectivity was quantitatively assessed by calculating the number of significant voxels in connectivity maps at baseline and following the fifth consecutive day of rTMS and suprathreshold voxels were recorded in the left and right motor cortices, as well as the supplementary motor area (SMA). These suprathreshold voxel counts were also normalized by the number of voxels in a given anatomical region.

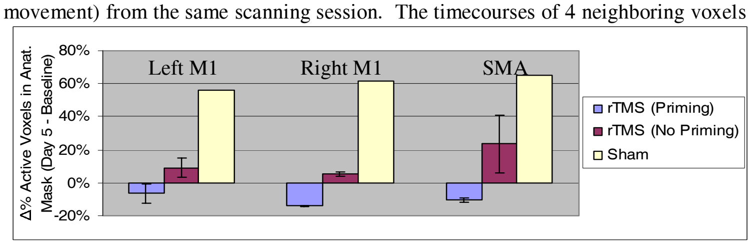

Fig. 1: Difference from baseline to day 5 in percent suprathreshold voxels in anatomical masks exhibit reduction for primed rTMS, slight increase for unprimed rTMS and more substantial increase for sham rTMS. Primed and unprimed rTMS results show average for two subjects in each group with bar to denote individual reductions.

RESULTS AND DISCUSSION A previous study from the same scanning session revealed that stimulus-induced BOLD activation showed reduction on day 5 relative to baseline scans for subjects receiving rTMS but was unable to distinguish primed and unprimed rTMS effects [4]. However, resting state data demonstrates reduced connectivity only for subjects receiving primed rTMS in the left and right M1, as well as SMA. As shown in Fig. 1, where connectivity changes are expressed as Δ% (difference in percent suprathreshold voxels in anatomical mask from baseline to day 5 of rTMS), connectivity maps exhibit a decrease in number of connected voxels for all three anatomical ROIs for subjects receiving primed rTMS but a slight increase for subjects receiving unprimed rTMS and a substantial increase for the subject receiving sham rTMS. The largest average connectivity decrease for primed rTMS subjects was evident in the right motor cortex (contralateral to seed and rTMS application; both subjects decreased by 14%) implying that bilateral connectivity could be more inhibited following primed relative to unprimed rTMS. The reduction in the number of voxels within the left motor cortex and SMA further suggests that localized primed rTMS may have an inhibitive effect on brain regions both distal and proximal to the site of rTMS application. For instance, the connectivity map for one subject receiving primed rTMS demonstrates a global reduction in suprathreshold voxels immediately following five consecutive days of rTMS relative to baseline (Fig. 2). The potential difference between the effect of primed and unprimed low frequency rTMS could be critical to future studies.

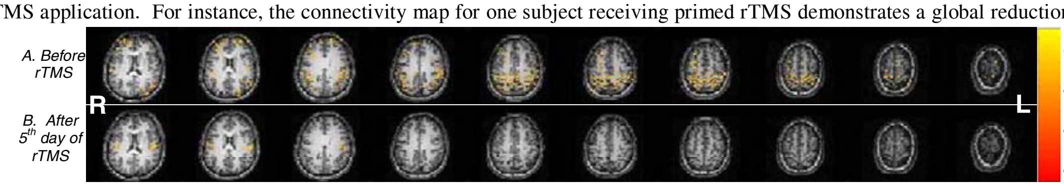

Fig 2: Connectivity maps at (A) baseline and (B) after the fifth consecutive day of rTMS demonstrate reduced connectivity (r>.65).

CONCLUSION The results imply that low-frequency (1 Hz) rTMS following a 6 Hz primer may more effectively reduce resting connectivity than unprimed 1 Hz rTMS compared to sham stimulation. Furthermore, brain regions distant to the target of stimulation, including SMA and contralateral M1, appear to have reduced connectivity relative to the site of primed low-frequency rTMS.

ACKNOWLEDGEMENTS This work was supported in part by the NIH RO1 EB002009, NS 40984 and Atlanta VA Rehabilitation Research and Development Center of Excellence. Thanks to Scott Peltier.

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