Increased Change in Water Dffusion MRI following Low frequency Repetitive Transcranial Magnetic Stimulation

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Objective: To examine whether diffusion-weighted imaging (DWI) technique can detect inhibitory cortical changes elicited by low frequency repetitive transcranial magnetic stimulation (rTMS).

Backgrounds: Low frequency rTMS induces inhibition of the cortical excitability, which can last well beyond the end of stimulation. DWI is a useful tool for measuring microscopic states of the brain tissue by probing water diffusion. Recently, this technique has been shown to detect alteration in water diffusion accompanied by cortical activation [2]. We hypothesized that DWI can also visualize rTMS-induced inhibitory cortical changes. Previous reports that applied rTMS outside a MRI scanner showed conflicting results [1, 3]. In the present study, we tested if DWI can detect rTMS-induced inhibitory cortical alternation by using a TMS/MRI combined method.

Methods: Twelve healthy volunteers received rTMS at 0.9 Hz for 10min at 90% of the motor threshold applied over the left primary hand motor area ($M1_{HAND}$) within a 3-T MR scanner (Trio, Siemens, Erlangen, Germany). Sets of diffusion-weighted MR images were collected prior (twice) rTMS application and 0min, 10min and 20 min following the rTMS application (named as *pre*, *post1*, *post2*, *post3* respectively)). The diffusion sequence consisted in a twice-refocused spin-echo echo-planar imaging (EPI) sequence sensitized to diffusion by an interleaved pair of bipolar magnetic field gradient pulses. Acquisition parameters were as follows: 2 mm thickness with no gap x 20 slices, pixel size = 2^2 mm^2, 87 ms echo time, 3000 ms repetition time, 1,302 Hz bandwidth. Two *b* values (*b* = 300 and 1,200 s/mm^2) were chosen to calculate apparent diffusion coefficient (ADC). The gradient pulse was applied with only (x, y, z)=(1, 1, 1) direction, since diffusion anisotropy was not expected in gray matter [2]. The ADC Images were calculated on a voxel-by-voxel basis from $[\ln(S_{b300}/S_{b1200})]/900$ and analyzed with the statistical parametric mapping software (SPM2). ADC changes between data sets before and after rTMS were statistically determined by a voxel-by-voxel one-way ANOVA. Group analysis was performed using a random effects model. An MP-RAGE acquisition (0.95^3 mm^3) was also run for anatomical reference.

Results: Following the rTMS, water diffusion was significantly increased in bilateral multiple motor areas including the stimulated M1 (Figure 1). The water diffusion increase in the stimulated M1 was recovered within 10 min (Figure 2a,) while that of some remote areas in contra lateral hemisphere remained for 10-20 min (Figure 2b).

Discussion: We found that rTMS applied over M1 increased water diffusion within an extended motor network. Not only was diffusion increased in the stimulated M1, but ADC increases were also found in the contra lateral hemisphere. Those remote ADC changes were long lasting (up to 20 minutes after stimulation). These findings demonstrate that rTMS conditioning effects induce cortical changes of extended motor network systems. Taking into account the observation that cortical water diffusion decreases during *activation* [2], possibly related to neuronal swelling, the current (opposite) findings might well reveal rTMS-induced cortical *inhibition*. This increase diffusion could reflect cellular changes (e.g. relative cell 'shrinking' in the affected network compared to baseline).

Reference

1. Duning T et al, 2004. Neurology; 62(11): 2144.

2. Le Bihan D et al, 2006. PNAS; 103(21): 8263-8.

3. Mottaghy FM et al, 2003. Neurology; 60(9): 1539-41.

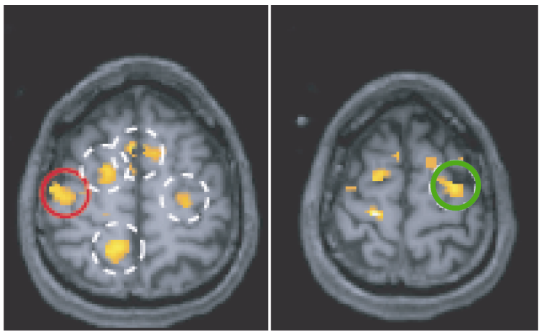

Figure 1. Statistical parametric maps revealing increase of water diffusion after the rTMS intervention (*pre* < *post1*). The change was found in multiple motor regions including in the stimulated M1HAND (red circle).

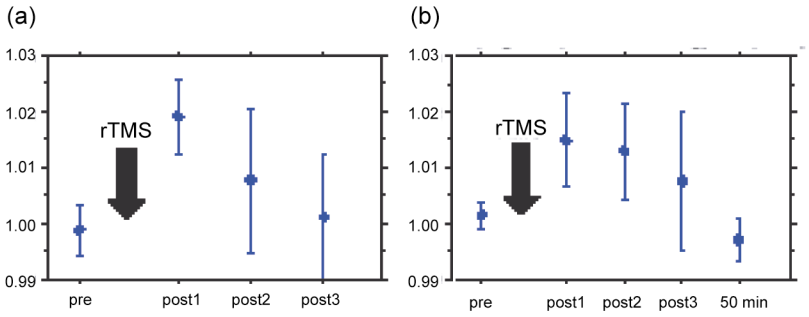

Figure 2. Time course of water diffusion relative to *pre*. (a) The alternation of the stimulated M1 (red circle in Fig. 1) was recovered within 10 min. (b) Increased water diffusion of the right premotor cortex (green circle in Fig. 1) kept for longer than 10 min. The values of some subjects (4/11 subjects) sustained over 20 min, which recovered within 50 min.