Imaging the immediate impact of transcranial magnetic stimulation using functional magnetic resonance imaging at 3T

S. Bestmann[1], J. Baudewig[1], H. Siebner[2], J. Rothwell[3], J. Frahm[1]

[1]Max Planck Institut für biophysikalische Chemie, Biomedizinische NMR Forschungs GmbH, Göttingen, Germany, [2]Department of Neurology, University of Kiel, Kiel, Germany, [3]Institute of Neurology, Sobell Department of Motor Neuroscience and Movement Disorders, London, United Kingdom

Purpose:

Despite the increasing use of transcranial magnetic stimulation (TMS) for investigations of motor cortex physiology and the causality between brain function and behaviour there is considerable lack of knowledge regarding the cortical underpinnings. Amounting evidence indicates that TMS is capable to modulate both local and remote brain regions. Recently, combined TMS-fMRI has been shown to allow the visualisation of the immediate impact of TMS-evoked activity changes [1,2]. Most studies, however, were restricted to low-frequency stimulation (1Hz), or constrained by low spatial resolution. Here, we implemented combined TMS-fMRI at 3T, thus profiting from increased BOLD sensitivity that allowed for a more thorough investigation of focal and remote brain activity changes induced by both supra- and subthreshold TMS.

Method:

Eleven healthy subjects were investigated after giving written informed consent and in accordance to the Declaration of Helsinki and local ethics board approval. Experiments were conducted at 2.89T (Siemens Trio, Erlangen, resonance frequency 123.234MHz). Functional MRI was conducted using a T2*-weighted single-shot, blipped gradient-echo EPI sequence (frequency-selective fat suppression, TR/TE= 3320/36ms, flip angle 70º, 128x128 matrix size, 2x2mm^2 in-plane resolution, 4mm section thickness, 20 oblique sections). Anatomical T1-weighted images were acquired using a short-echo time 3D FLASH sequence (TR/TE=11/4.92ms, flip angle 15º, 1x1x1mm^3 isotropic resolution). Repetitive TMS (rTMS) was conducted at 110% of individual resting motor threshold (RMT) or 90% of individual active motor threshold (AMT) over the left sensorimotor cortex (M1/S1) using a non-ferromagnetic figure-of-eight coil (70mm outer wing diameter). Biphasic TMS pulses were interleaved with fMRI but completely separated from image acquisition periods [3,4,5]. Paradigms comprised eight cycles of rTMS (9960ms, 3.125Hz) and rest periods (23240ms). Furthermore, motor regions were located by auditory-cued dorsi-flexion of the right index finger. The nature of rTMS was confirmed by simultaneous electromyographic recordings from the target muscle (Brain Products, Munich, Germany). Imaging data analysis and visualisation was performed using GLM (BrainVoyager 2000, Brain Innovation, Maastricht, The Netherlands).

Results:

None of the subjects reported any side effects. Suprathreshold rTMS evoked clear electromyographic activity in the target muscle, whereas no such activity was observed during subthreshold rTMS. No image perturbations were evidenced during rTMS.

Suprathreshold rTMS evoked activity within the left M1/S1, PMd, PMv, bilateral SMA, and dorsal cingulate motor area (CMA), and ipsilateral (right) antero-dorsal cerebellar lobule (Fig. 1). A decreased BOLD signal was observed in contralateral M1/S1. At the subcortical level, activations in the left thalamus and the lentiform nucleus (ventro-medial postcommissural portion of the putamen) were also detected. Widespread bilateral activity was shown in the primary and secondary auditory, the inferior colliculi and the medial geniculate nucleus.

Subthreshold rTMS evoked activity in bilateral SMA, CMA, and left PMd. No significant response was found at the site of stimulation. Activity changes were also found in the left and right ventro-lateral thalamus, while no activity could consistently be detected in the striatum. Direct comparison of sub- and suprathreshold TMS yielded significant differences in several motor regions, but not in auditory cortical or subcortical areas (Fig. 2).

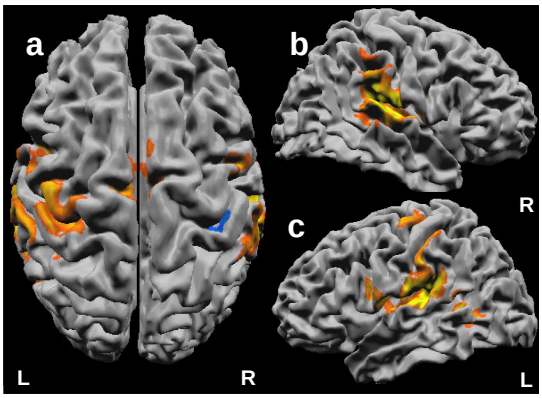

Figure 1: Significant suprathreshold rTMS-related increases in BOLD contrast signal (p<0.01, corrected), projected on a 3D dorsal **(a)** and lateral **(b, c)** view of a reconstruction of a template brain (Montreal Neurological Institute, MNI). Strong activity was found in left M1/S1, PMd, PMv, bilateral SMA, auditory cortices, SI and SII. On the left hemisphere, additional activity was found along the inferior precentral sulcus. Decreased BOLD contrast signal was evidenced in the right M1/S1. L: left, R: right.

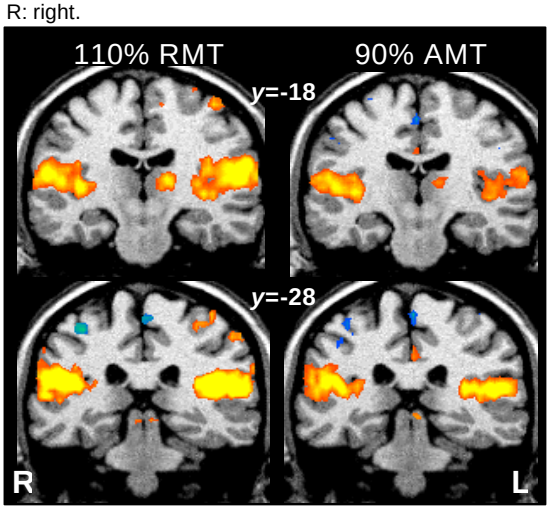

Figure 2: Comparison of BOLD contrast signal changes evoked by suprathreshold rTMS **(left)** and subthreshold rTMS **(right)**. Apart from strong auditory activation, suprathreshold rTMS induced activity in the left M1/S1 and left thalamus. Subthreshold rTMS evoked activity in the left thalamus but not in the left M1/S1. Negatively correlated signal right M1/S1 was observed in both conditions.

Conclusions:

The data for the first time demonstrates the feasibility of interleaved TMS and fMRI at 3T. As such, it is a powerful new technique to visualise the immediate impact of cortical stimulation in local and remote brain regions. The data illustrates the capability of TMS to evoke activity changes in distinct networks even at subthreshold intensities. Therefore, these cannot be attributed to re-afferent processing from peripheral muscle movements or spinal processes. The lack of local responses during subthreshold rTMS implies a threshold for the occurrence of local BOLD responses, similar to the notion of a sigmoid relationship between synaptic activity and changes in cortical hemodynamics [6]. Noteworthy, TMS is accompanied by auditory and somatosensory stimulation that is not easily controlled for. Although it may lead to confounding activity, the present data demonstrates that, at least for the motor system, such activations can be distinguished from motor-related activity.

References:

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