

BOLD IMAGING OF INHIBITION AND FACILITATION INDUCED BY PAIRED-PULSE TRANSCRANIAL MAGNETIC STIMULATION: FEASIBILITY AND REPRODUCIBILITY

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Introduction

Paired-Pulse Transcranial Magnetic Stimulation (TMS) can be used to study cortical excitability. Short interstimulus intervals (ISIs; 1-4 ms) inhibit while longer ISIs (6-15 ms) facilitate motor evoked potentials (MEPs) induced by the TMS test pulse to the primary motor cortex [1]. Recently, the feasibility of interleaving TMS with functional magnetic resonance imaging (fMRI) was demonstrated [2, 3]. The combination of paired pulse TMS with fMRI provides a unique possibility to directly visualize TMS induced changes in excitability at a high spatial and temporal resolution.

Methods

TMS was carried out using two Magstim Rapid stimulators, a custom built bistimulation module, and a special MR compatible non-ferromagnetic figure-of-eight coil connected via an eight meter cable to the stimulators outside the scanner room [4]. Before starting the simultaneous TMS and fMRI experiment, the optimal position of the coil for evoking movements of the right hand (referred to as motor hot spot) was determined. Motor thresholds were then obtained with single TMS pulses. Resting motor threshold (RMT) was defined as the minimum intensity that evoked a muscle twitch in 5 out of 10 trials. The minimum intensity that caused an observable muscle twitch during 10% of maximum voluntary contraction in 5 out of 10 trials was defined as active motor threshold (AMT). Electromyographic (EMG) responses were recorded from the right first dorsal interosseous (FDI) muscle. Cortical excitability was tested in the relaxed FDI using the Kujirai paradigm [1]: conditioning-test pulse pairs with a short, inhibitory ISI (3 ms, TMS_{short}) or long, facilitatory ISI (12 ms, TMS_{long}) were applied whereat the conditioning pulse intensity was set to a sub-threshold level (90% AMT) and the test pulse was given at suprathreshold intensity (110% RMT). The design of the principal part of the study was chosen as typical block-design as often performed in fMRI experiments: 10 pulse pairs or 10 single test pulses (TMS_{single}) were applied at 0.5 Hz in 20s and these blocks were separated by control periods.

BOLD fMRI was performed at 3 Tesla (Siemens Trio) using EPI (TR 2000ms, TE 36ms, 20 slices, 2x2x4mm³). The TMS pulses were applied at the beginning of 200 ms temporal gaps between volume acquisitions in order to avoid image disturbances. During 3 fMRI runs each 20s block (TMS_{short}, TMS_{long}, TMS_{single}) was performed 4 times in a pseudo-randomised order separated by 40s lasting resting periods. In order to assess the reproducibility the whole experiment was repeated 5 months later.

Results

During both sessions RMT (84% resp. 85% of the maximum output from stimulator 1) and AMT (83% resp. 84% from stimulator 2) were almost identical. The unusual high AMT compared to the RMT is due to the different powers of the 2 stimulators. **Figure 1** demonstrates the facilitation as shown by the increased MEP amplitude (green lines) when using long ISIs (TMS_{long}). Short ISIs (red lines) induced only a mild reduction of the MEP compared to the single test pulse. fMRI activation maps calculated by contrasting suprathreshold TMS to the resting periods revealed activations in bilateral pre-motor areas, left sensory-motor cortex, supplementary motor cortex and bilateral secondary sensory and auditory cortex in both sessions (**Figure 2**). The amplitude of the fMRI response was higher during facilitatory TMS pulse pairs (TMS_{long}, green lines) compared to the inhibitory TMS (TMS_{short}, red lines, **Figure 3**).

Discussion

The EMG results verified the inhibitory and facilitatory effects of subthreshold conditioning TMS pulses in a typical fMRI suitable block-design. Suprathreshold TMS of the primary motor cortex during fMRI resulted in activation of cortical and subcortical structures which are part of the motor network. This activation pattern is highly reproducible as demonstrated in Figure 2. Facilitating pulse pairs (TMS_{long}) not only induced an enlarged EMG response but also lead to an increased BOLD signal. Short ISIs (TMS_{short}) resulted in slightly decreased EMG amplitudes whereas an inhibition of the BOLD signals could not be observed. This might be caused by a reduced metabolic demand of inhibition compared to excitation [5]. In summary, we demonstrated for the first time that paired-pulse TMS during fMRI is feasible and bears the unique potential to study experimental manipulations of cortical excitability using neuroimaging methods.

References

[1] Kujirai et al.: Corticocortical inhibition in human motor cortex. J Physiol, 1993 [2] Bohning et al.: Central Echo-planar BOLD fMRI of brain activation induced by concurrent transcranial magnetic stimulation. Invest Radiol, 1998. [3] Baudewig et al.: Regional modulation of BOLD MRI responses to human sensorimotor activation by transcranial direct current stimulation. Neuroreport, 2001. [4] Bestmann et al.: On the synchronization of transcranial magnetic stimulation and functional echo-planar imaging. JMRI, 2003. [5] Waldvogel et al.: The relative metabolic demand of inhibition and excitation. Nature. 2000

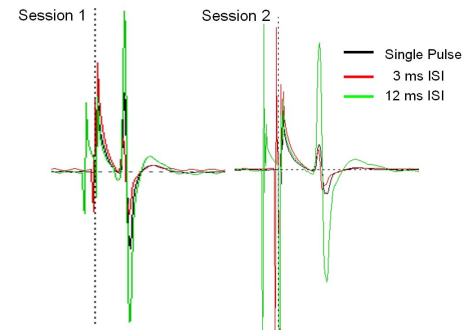


Figure 1: EMG responses in the FDI during both sessions. At the dotted line a TMS artifact due to the test pulse is clearly visible. Additionally, artifacts due to the conditioning pulse could be detected prior the test pulse. A pronounced facilitation (green line, TMS_{long}) and less inhibited response (red line, TMS_{short}) were found in the MEP.

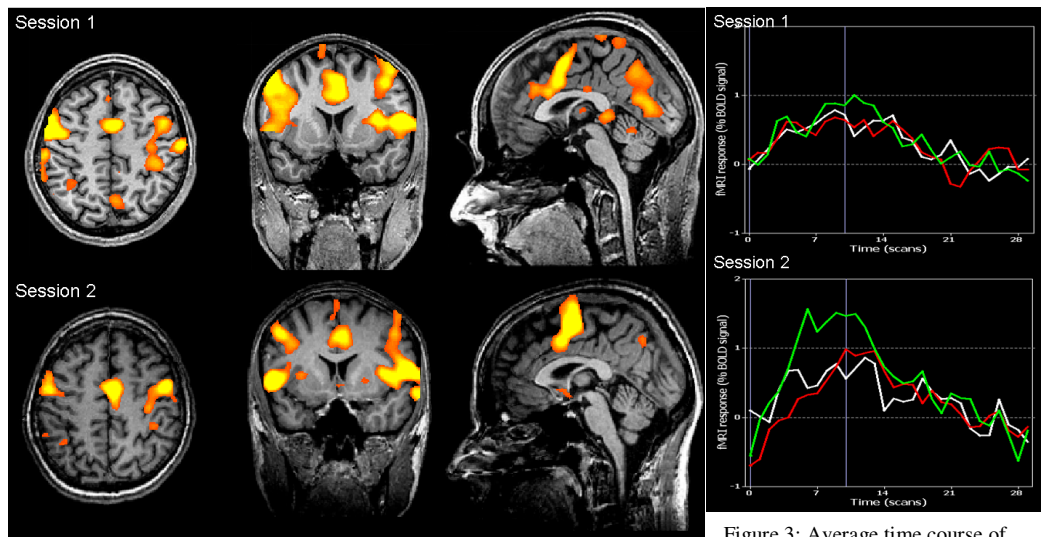


Figure 2: Activation by suprathreshold TMS of the left primary motor cortex in 2 separate sessions.

Figure 3: Average time course of signals from the stimulated sensory-motor cortex. green = TMS_{long}, red = TMS_{short}, white = TMS_{single}