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TIME COURSE OF BLOOD OXYGENATION LEVEL–DEPENDENT SIGNAL RESPONSE AFTER THETA BURST TRANSCRANIAL MAGNETIC STIMULATION OF THE FRONTAL EYE FIELD

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Abstract—The aim of the current study was to examine the effect of theta burst repetitive transcranial magnetic stimulation (rTMS) on the blood oxygenation level–dependent (BOLD) activation during repeated functional magnetic resonance imaging (fMRI) measurements. Theta burst rTMS was applied over the right frontal eye field in seven healthy subjects. Subsequently, repeated fMRI measurements were performed during a saccade-fixation task (block design) 5, 20, 35, and 60 min after stimulation. We found that theta burst rTMS induced a strong and long-lasting decrease of the BOLD signal response of the stimulated frontal eye field at 20 and 35 min. Furthermore, less pronounced alterations of the BOLD signal response with different dynamics were found for remote oculomotor areas such as the left frontal eye field, the pre-supplementary eye field, the supplementary eye field, and both parietal eye fields. Recovery of the BOLD signal changes in the anterior remote areas started earlier than in the posterior remote areas. These results show that a) the major inhibitory impact of theta burst rTMS occurs directly in the stimulated area itself, and that b) a lower effect on remote, oculomotor areas can be induced.

Key words: saccades, FEF, PEF, humans, fMRI, TMS.

Repetitive transcranial magnetic stimulation (rTMS) is an established non-invasive method, which allows inducing transient plastic changes in the human cortex. Depending on the stimulation parameters of rTMS, inhibitory or facilitatory behavioral changes can be achieved in motor, oculomotor, and several higher-cognitive systems (Kobayashi and Pascual-Leone, 2003; Hallett, 2000; Lisbany et al., 2002; Rossi and Rossini, 2004; Nyffeler et al., 2006a).

In general, inhibitory effects result from application of low frequency rTMS, whereas facilitation is induced by application of high frequency rTMS (>5 Hz) (for a review, see Hallett, 2000; Chen et al., 1997; Maeda et al., 2000). The duration of these rTMS effects is rather short, i.e. in the range of several minutes. Recently, an rTMS protocol has been proposed that generates a much longer lasting interference with cortical functioning. Huang and colleagues (2005) showed that application of a continuous train of theta burst rTMS over the motor cortex induced a long-lasting inhibition of the motor evoked potential. We recently demonstrated that theta burst rTMS over the frontal eye field (FEF), a cortical oculomotor area involved in saccade execution (Pierrot-Deseilligny et al., 1995), had an inhibitory behavioral effect outlasting stimulation by 30 min (Nyffeler et al., 2006). Following theta burst rTMS, saccade latencies immediately and bilaterally increased, starting to decay after 10 min, returning to baseline level after another 20 min.

An important issue in rTMS research is whether and to which extent cortical stimulation has not only local but also remote effects. If changes in activity of a remote area are assumed to be the consequence of an altered state of the stimulated region, evidence of anatomical or task-specific functional relation between these regions should be found.

Studies combining low or high frequency rTMS with functional imaging such as positron emission tomography or functional magnetic resonance imaging (fMRI) have indeed demonstrated remote effects of rTMS (e.g. Paus et al., 1997; Bestmann et al., 2004; Ruff et al., 2006; Rounis et al., 2005, 2006; Sack et al., 2007; Taylor et al., 2007).

However, the correlation between excitatory or inhibitory stimulation protocols of rTMS and the regional cerebral blood flow (CBF) produced ambiguous results: studies using both inhibitory and excitatory rTMS protocols found an increased regional CBF in both conditions (Siebner et al., 2000; Strafella and Paus, 2001; Lee et al., 2003; Rounis et al., 2005).

Several fMRI studies have shown a positive correlation between the blood oxygenation level–dependent (BOLD) signal increase and the corresponding increase of neuronal activity in a cortical region (Logothetis et al., 2001; Smith et al., 2002; Thompson et al., 2003; Devor et al., 2003; Niessing et al., 2005). The possibility to induce long-lasting and well-defined behavioral changes by theta burst rTMS opens new perspectives to elucidate these issues by combining rTMS and fMRI. The aim of the present study was to analyze the temporal modification of the mean BOLD signal response of the cortical oculomotor

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Abbreviations: BOLD, blood oxygenation level–dependent; CBF, cerebral blood flow; CF, central fixation point; FEF, frontal eye field; fMRI, functional magnetic resonance imaging; PEF, parietal eye field; rTMS, repetitive transcranial magnetic stimulation; SEF, supplementary eye field; T, lateral target.

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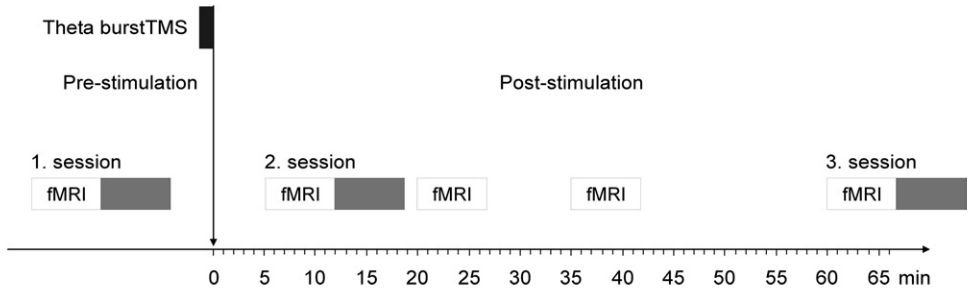

Fig. 1. Schematic study design. Five consecutive measurements were performed, one before and four after stimulation (5, 20, 35, and 60 min after stimulation). Gray bars represent high-resolution 3-D anatomy, which was acquired for co-registration.

network after theta burst rTMS of the right FEF by repeated fMRI sessions.

EXPERIMENTAL PROCEDURES

Subjects

Seven healthy subjects with normal or corrected to normal vision were investigated. Mean age was 31 years (S.D.=9 years), four of the participants were females, two left-handed. The study was approved by the ethical committee of the State of Bern and is consistent with the latest Declaration of Helsinki. Prior to participation, all subjects gave written informed consent.

Study design

In order to interfere with the oculomotor network, the right FEF was stimulated using a theta burst rTMS protocol (Nyffeler et al., 2006a,b). A block design (saccadic eye movements versus fixation) was performed with five scanning measurements (Fig. 1).

The subjects' BOLD responses were acquired in three separate fMRI sessions: a first session before stimulation and a second session with data acquisition 5, 20, and 35 min after stimulation. Then, subjects left the scanner to avoid the inconvenience of long in-scanner time. Finally, a last fMRI session was performed 60 min after stimulation. In each session, a high-resolution 3-D anatomy acquisition was taken for co-registration.

Saccade paradigm

A flashed overlap paradigm (Fig. 2) was presented using the E-prime® presentation software (Psychology Software Tools Inc., www.pstnet.com). First, a central fixation point (CF, red asterisk) was presented on a light gray background. After a pseudo-randomized duration of 500, 1000, or 1500 ms—pre-defined in the E-prime® stimulation protocol—a lateral target (T, red asterisk) was flashed for 120 ms at 9° left or right from the CF. The CF remained visible during the presentation of the lateral target (T). E-prime® software was triggered by the TTL signal of the MR scanner. Thus, stimulus presentation and the corresponding functional volume were synchronized. Subjects were instructed to perform a saccade to the position where the T was flashed and then to re-fixate the CF. Saccades were performed in blocks of 10 saccades, synchronized to the scanning volumes. During each block, five saccades to the left and to the right side were performed. The order of left- vs. rightward saccades was pseudo-randomized. Between each saccade block, a fixation block was intersected, presenting a blue asterisk as CF.

TMS procedure

A TMS stimulator (MagPro, Medtronic Functional Diagnostics, Skovlunde, Denmark) was used to generate repetitive biphasic magnetic pulses. The pulses were delivered with a figure-eight-coil (magnetic coil transducer MC-B70, Medtronic) with an outer radius of 50 mm.

In the first session, single pulse TMS was used to localize the right FEF according to previously described procedures (e.g. Müri et al., 1991; Ro et al., 1999). In brief, the optimal site and individual resting motor threshold for the subject's relaxed small hand muscles were determined by stimulating the right motor cortex with single pulses. The coil was then moved 2 cm anteriorly from the hand area. The handle of the coil pointed backwards (45° angle to the sagittal line). Finally, the localization of the presumed right FEF was marked with a vitamin-E capsule. Vitamin E is an oily solution providing excellent contrast in the T1-weighted gradient echo images. During the first session, the correspondence between the locations of the FEF as localized by TMS and the site of FEF activation was verified using the online fMRI analysis tool of the Siemens scanner software.

Before the second session, one continuous train of theta burst rTMS was applied (600 pulses in total; a burst of three pulses with 30 Hz was repeated with intervals of 100 ms between bursts; see Nyffeler et al., 2006a,b) over the right FEF. During stimulation, the examiner held the coil and subjects were asked to keep their eyes closed. Theta burst rTMS was delivered at 80% of the individual subject's resting motor threshold.

fMRI method and MR scanning parameters

A 3-T whole-body MRI system (Siemens Trio TIM, Siemens Medical Systems, Erlangen, Germany) was used for the investigation. Thirty-five axial slices (3 mm slice thickness, 25% interslice distance) covering the whole brain were acquired parallel to the anterior/posterior commissure for functional imaging (repetition

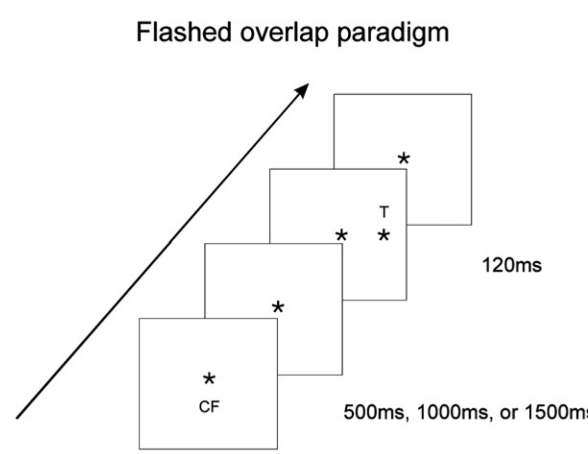

Fig. 2. Saccade paradigm. The CF was presented throughout the presentation. The T was flashed for 120 ms in a pseudo-randomized order 9° to the left or right of the CF.