Inhibitory Transcranial Magnetic Theta Burst Stimulation Attenuates Prefrontal Cortex Oxygenation

Sara V. Tupak,^{1,*} Thomas Dresler,¹ Meike Badewien,¹ Tim Hahn,^{1,2}
Lena H. Ernst,³ Martin J. Herrmann,¹ Jürgen Deckert,¹
Ann-Christine Ehlis,³ and Andreas J. Fallgatter³

¹Department of Psychiatry, Psychosomatics, and Psychotherapy, University Hospital Wuerzburg, Germany

²Department of Cognitive Psychology II, Johann Wolfgang Goethe University Frankfurt/Main, Germany

³Department of Psychiatry and Psychotherapy, University Hospital Tuebingen, Germany

Abstract: Recent studies highlighted the great potential of newly established theta burst stimulation (TBS) protocols for non-invasive human brain stimulation studies using transcranial magnetic stimulation (TMS). While intermittent TBS over the primary motor cortex was found to potentiate motor evoked potentials, continuous TBS led to profound attenuations. Although numerous studies investigated the impact of TBS on motor cortex function, yet, only few imaging studies focused on its effects in other brain areas. Particularly for the prefrontal cortex, it is unclear whether TBS has similar effects compared to application over motor areas. In the current study continuous TBS was applied to either the left or right dorsolateral prefrontal cortex in a sample of healthy subjects. Changes in prefrontal oxygenation were measured during an emotional Stroop task by means of functional multi-channel near-infrared spectroscopy (fNIRS) before and after stimulation. Results showed bilaterally decreased prefrontal oxygenation following inhibitory stimulation of the left prefrontal cortex but no behavioral effect. No such alterations were observed following right-hemispheric or sham stimulation. The results of the current study are in line with earlier findings and additionally demonstrate that also prefrontal oxygenation can be impaired by continuous TBS. *Hum Brain Mapp* 34:150–157, 2013. © 2011 Wiley Periodicals, Inc.

Key words: DLPFC; emotional Stroop task; NIRS; prefrontal cortex; TBS; TMS

INTRODUCTION

About 25 years ago, Barker et al. [1985] showed that motor-evoked potentials (MEPs) of the hand and leg can

be elicited through magnetic stimulation of the primary motor cortex, marking the beginning of human brain stimulation research. During transcranial magnetic stimulation (TMS), a brief electrical current is passed through a coil

Ann-Christine Ehlis and Andreas J. Fallgatter contributed equally to this work.

Contract grant sponsor: Deutsche Forschungsgemeinschaft (DFG; Sonderforschungsbereich "Fear, Anxiety and Anxiety Disorders"); Contract grant number: SFB TRR58C4.

*Correspondence to: Sara V. Tupak, Psychophysiology and Functional Imaging, Department of Psychiatry, Psychosomatics and Psychotherapy, University Hospital Wuerzburg, Fuechsleinstrasse 15, 97080 Wuerzburg, Germany.

E-mail: Tupak_S@klinik.uni-wuerzburg.de

Received for publication 16 June 2011; Accepted 7 July 2011

DOI: 10.1002/hbm.21421

Published online 14 October 2011 in Wiley Online Library (wileyonlinelibrary.com).

thereby generating a magnetic field perpendicular to it. Placed on the head, this field penetrates the underlying skull and tissue and impacts neuronal activity within the cortex [Hallett, 2000]. Directly observable reactions can be elicited by single pulse TMS, e.g., MEPs when applied to primary motor cortex [Barker et al., 1985], visual phosphenes over primary visual cortex [Meyer et al., 1991], and disturbances in speech production over Broca's [Pascual-Leone et al., 1991] and Wernicke's area [Knecht et al., 2002]. Longer lasting alterations of focal neuronal activity are accomplished through repeated application of magnetic pulses (known as repetitive (r)TMS). Low-frequency (≤ 1 Hz) rTMS is commonly assumed to induce temporary neuronal inhibition whereas high-frequency (≥ 10 Hz) stimulation has been shown to have excitatory effects [Hallett, 2000]. An exception is the recently developed theta burst stimulation (TBS) protocol by Huang et al. [2005]. Emanated from years of electrophysiological animal research [e.g., Hess and Donoghue, 1996; Hyman et al., 2003], they transferred the findings of induced long-term depression or potentiation following electrical stimulation within the theta-frequency range of rodents' hippocampal and primary motor neurons to human research. Two protocols were evolved, an intermittent (iTBS) and a continuous TBS (cTBS) paradigm. Although both protocols partly consist of high-frequency stimulation (50 Hz), cTBS has been found to have attenuating effects on MEPs when applied to primary motor cortex, while MEP amplitudes were potentiated following iTBS. A third protocol, intermediate TBS (imTBS), produced no specific effects. A general advantage of those TBS protocols is the duration of their effects (~ 60 min for cTBS and ~ 20 min for iTBS) that greatly exceed the relatively short time of application [< 1 min for cTBS and < 4 min for iTBS; Huang et al., 2005].

To date, only few studies investigated the effects of TBS by means of neuroimaging methods such as electroencephalography [EEG; Grossheinrich et al., 2009], positron emission tomography [PET; Ko et al., 2008], functional magnetic resonance imaging [fMRI; Hubl et al., 2008], and functional near-infrared spectroscopy [fNIRS; Mochizuki et al., 2007]. Most research, however, focused on primary motor cortex since effects in those areas are directly assessable by? electromyography [EMG; for a review see Cárdenas-Morales et al., 2010].

The primary purpose of the current study was to investigate whether cTBS impedes prefrontal activity and if this cortical inhibition can be tracked by multi-channel fNIRS. fNIRS measures regional cortical changes in oxygenated (O_2Hb) and deoxygenated hemoglobin (HHb), both of which are assumed to reflect ongoing brain activity [for detailed information see Jöbsis, 1977; Obrig and Villringer, 2003; Strangman et al., 2002a]. Using fNIRS for the detection of hemodynamic TBS effects has two main advantages. First, preparation time is relatively short (< 10 min) which assures that TBS effects are not outlasted by the measurement procedure. Second, it has no side effects thereby enabling repeated-measurement designs. In addition,

it is relatively insensitive to movement artifacts [Schecklmann et al., 2010] and measurements can be conducted in a quiet and natural environment without head fixation.

As indicated by Mochizuki et al. [2007], the inhibitory effects of cTBS exert their effects primarily in terms of reduced O_2Hb levels. The authors observed decreased oxygenation in the contralateral site of stimulation and neighboring areas (i.e. cTBS over primary sensory cortex led to reduced O_2Hb signals in contralateral primary sensory and motor cortices). Similar results in terms of an ipsilateral decrease in the blood oxygen level dependent (BOLD) response were obtained in an fMRI study following cTBS over the right frontal eye field [Hubl et al., 2008]. To date, those are the only studies investigating hemodynamic effects of TBS.

Our secondary aim was to assess whether prefrontal cortex (PFC) inhibition in turn leads to specific interference during emotional word processing. Hemodynamic changes were recorded during the performance of an emotional Stroop task [Williams et al., 1996]. In this task, subjects indicated the font color of anxiety and neutral words while reaction times were recorded. A specific attentional bias with increased latencies for emotionally negative (e.g., threatening, disorder-related) compared to neutral words has repeatedly been shown for various kinds of anxiety disorders [e.g., Lundh et al., 1999; Williams et al., 1996] and subjects with elevated trait anxiety [for a review see Bar-Haim et al., 2007]. Among healthy subjects, such bias was found less reliably [e.g., Dresler et al., 2009b; Thomas et al., 2007]. On the neuronal level, processing of negative words activated the dorsolateral PFC [DLPFC; Compton et al., 2003]. Moreover, the PFC seems to represent a critical structure exerting top-down control during this task [Dresler et al., 2009a]. D'Alfonso et al. [2000] applied low-frequency rTMS to either the left or right PFC prior to a pictorial emotional Stroop task. Inhibition of the right but not left PFC resulted in an attentional bias towards angry faces. This result is also supported by recent fMRI studies that evaluated the potential top-down control of prefrontal structures on the limbic system to regulate negative emotions [Ochsner et al., 2004] and anxiety [for a review see Berkowitz et al., 2007; Kalisch et al., 2006]. Especially during cognitive processing of threatening stimuli, PFC and amygdala activity seem to be inversely related [Hariri et al., 2000, 2003].

To summarize, in the current study we applied active or sham cTBS to either the left or right DLPFC in a sample of healthy subjects and measured both behavioral and hemodynamic reactions before and directly after stimulation. We expected to observe a significant decrease in O_2Hb levels following active TBS. Further, we hypothesized that PFC inhibition will cause impaired processing of anxiety words during an emotional Stroop task. More precisely, we assumed that active cTBS will lead to a potentiated attentional bias towards anxiety words in terms of increased reaction times and error rates.

MATERIALS AND METHODS

Subjects

In total, 51 right-handed volunteers participated in the current study (34 females, mean age: 23.14 ± 2.59 years). Except for one participant, who reported a dysthymic episode in the past, none of the subjects had a history of psychiatric or neurological illness according to a self-report screening questionnaire based on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders [First et al., 2002]. Exclusion criteria were current pregnancy or rTMS contraindications (i.e., epilepsy, heart disease, magnetizable implants within the head).

Because rTMS over frontal areas may impact mood [Dearing et al., 1997], state anxiety, state anger, and mood were monitored before and after the experiment by means of the state subscales of the State-Trait Anxiety Inventory [STAI; Laux et al., 1981], State-Trait Anger Expression Inventory [STAXI; Schwenkmezger et al., 1992], and Positive and Negative Affect Schedule [PANAS; Krohne et al., 1996]. To assess anxiety sensitivity, subjects filled in the German version of the Anxiety Sensitivity Index [ASI; Alpers and Pauli, 2001].

All participants gave written informed consent and were TMS-naïve. The present study was approved by the ethics committee of the University of Wuerzburg and is in accordance with the declaration of Helsinki from 2008. The sample was randomly divided into three subgroups: cTBS over the left DLPFC ($N = 16$), right DLPFC ($N = 16$), or as a control group, sham cTBS ($N = 19$) counterbalanced for stimulation side.

Emotional Stroop Task

We presented 15 neutral and 15 anxiety words in a computerized emotional Stroop task using Presentation software (Neurobehavioral Systems, Albany, CA). Anxiety words were related to bodily symptoms and cognitions of acute fear (e.g., fear, danger, or dizziness). Words of the two conditions were comparable regarding the number of letters, number of syllables, and frequency in German written and spoken language (CELEX database). Each word was presented once in four different font colors (i.e., blue, green, yellow, and red), resulting in 120 trials in total. Trials were arranged in a random event-related design lasting between 6 to 10 s and started with a fixation cross for 500 ms. Stimulus duration was 1.5 s and the interstimulus interval randomly jittered between 4 and 8 s. Participants had to indicate the font color by pressing a corresponding button using their index and middle fingers of both hands. Color-button assignment was counter-balanced across subjects and measurements. In advance, subjects practiced the appropriate color-button assignment during 20 practice trials by responding to meaningless letter strings ('XXXXXXXX').

All subjects were measured twice, once at baseline before the application of cTBS and once afterwards. Fol-

lowing cTBS, half of the subjects directly performed the second run of the emotional Stroop task while the other half firstly performed another cognitive task for 9 min. The results of this task are not the focus of the present study and will be reported elsewhere. The time interval between the end of stimulation and the second run never exceeded 45 min.

fNIRS

Blood oxygenation parameters were recorded with a 52-channel continuous wave system (ETG-4000 Optical Topography System; Hitachi Medical Corporation, Tokyo, Japan). A flexible 3×11 channel probe set was strapped over the subjects' forehead so that the middle probe of the bottom row was positioned over Fpz according to the international 10–20 system for electrode placement [Jasper, 1958; Fig. 1]. Near-infrared light of two different wavelengths (695 ± 20 and 830 ± 20 nm) was emitted through the skull and underlying cortex by 17 semiconductor lasers. Relative changes in the reflected light were detected by 16 neighboring photo-detectors at a temporal resolution of 10 Hz. Inter-probe distance was 3 cm. The measured signal was transformed into relative changes of O_2Hb by a modified Beer-Lambert Law. Further details about the fundamentals of the fNIRS signal are described elsewhere [Obrig and Villringer, 2003].

CTBS

Following the emotional Stroop task, TMS was applied with a figure-of-eight coil (MC-B70, 80 mm diameter) by a Medtronic MagPro X100 stimulator (Medtronic MagPro, Duesseldorf, Germany). CTBS consisted of 200 high-frequency triple-bursts (50 Hz), delivered every 200 ms (5-Hz theta rhythm), summing up to 600 pulses in total [see Huang et al., 2005]. Stimulation sites were electrode positions F3 (left DLPFC) or F4 (right DLPFC) according to the international 10–20 system for electrode positioning [Jasper, 1958]. Active left- and right-hemispheric stimulation was applied at 80% resting motor threshold as measured over the respective left and right primary motor cortex. Sham cTBS was applied at 60% resting motor threshold by tilting the coil by 45° .

Data Analysis

Data analysis was performed using MATLAB (MathWorks, Natick, MA) and PASW Statistics (SPSS, Chicago, IL). The level of significance was set to $P = 0.05$ and statistical trends were reported for $P \leq 0.10$. Data were analyzed using the general linear model. For post hoc tests either one- or paired-sample t tests were used. If necessary, a Bonferroni correction was applied. For O_2Hb activation maps the false discovery rate (FDR) correction was used.

TABLE I. Sample characteristics

	Prior to cTBS			Following cTBS		
	Sham cTBS	Left cTBS	Right cTBS	Sham cTBS	Left cTBS	Right cTBS
Anxiety sensitivity (ASI)	14.9 (10.0)	16.1 (6.9)	13.9 (8.5)	—	—	—
State anxiety (STAI)	41.5 (4.3)	40.2 (6.6)	40.3 (3.4)	39.8 (4.9)	38.8 (6.1)	37.2 (8.8)
State anger (STAXI)	10.6 (1.6)	10.7 (1.4)	10.8 (1.6)	10.3 (0.7)	10.1 (0.3)	10.6 (1.3)
Positive affect (PANAS)	29.2 (4.4)	29.2 (4.6)	29.1 (3.9)	26.3 (5.5)	29.4 (8.0)	23.9 (6.2)
Negative affect (PANAS)	11.6 (1.7)	11.1 (1.3)	12.5 (2.2)	11.3 (2.2)	10.8 (1.4)	11.4 (1.8)

Mean scores and standard deviations for all groups prior to and following cTBS.

Trait Anxiety and Mood

Possible TMS induced changes in state anxiety, state anger, and positive and negative affect were analyzed by performing repeated measures analyses of variance (ANOVA).

Behavioral Data

Mean reaction times were calculated for all correct trials in each condition separately. Responses beneath or above two standard deviations from the mean were excluded from further analyses. In addition, error rates were taken as a second indicator for a potential emotional Stroop effect. Baseline data were analyzed by paired-sample *t* tests. CTBS effects were in turn investigated by performing repeated measures ANOVA. One subject was excluded from behavioral analyses because of a 33% error rate. All other subjects ($N = 50$) correctly identified at least 85% of all trials.

fNIRS

Data analysis focused on changes in O_2Hb because it has been shown that O_2Hb reacts more sensitively than HHb to changes in cerebral blood flow and TBS [Hoshi et al., 2001; Mochizuki et al., 2007; Strangman et al., 2002b]. Ten data sets were excluded after visual inspection and quality ratings by three of the authors due to insufficient data quality. Three additional subjects could not be included due to data loss resulting in final sample sizes of 13 (sham cTBS), 11 (left active cTBS), and 14 (right active cTBS) subjects.

A cosine and a moving average filter (time window: 5 s) were applied to remove slow drifts and the high frequency portion of the data. Hypothesis testing was performed on estimated beta weights calculated by using an ordinary least squares regression model. A Gaussian hemodynamic response function was fitted to the data with a peak time of 7.5 s [for details see Plichta et al., 2006, 2007]. To test whether frontal areas were sufficiently activated during the emotional Stroop task, O_2Hb activation maps were constructed by calculating one-sample *t* tests against zero for every channel and condition separately and paired-sample *t* tests for the contrast between conditions. For fur-

ther analyses, a priori determined bilateral DLPFC channels were averaged and taken as dependent variable (right DLPFC channels: 3, 13, 14, 24; left DLPFC channels: 8, 18, 19, 29; Fig. 1).

Exploratory analysis indicated a trend toward unexpected hemodynamic baseline differences between groups which could not be explained by any other collected data (demographics or psychometric data). Consequently, we added the grouping variable for baseline fNIRS analyses by means of repeated measures ANOVA. To compare hemodynamic activity between baseline and post-TBS measurements, repeated measures ANOVAs were performed for each experimental group separately to obviate possible confounding due to baseline differences.

RESULTS

Trait Anxiety and Mood

Means and standard deviations for all questionnaires are displayed in Table I. A “Time” (pre vs. post cTBS) $\times$ “Group” (sham vs. left active vs. right active cTBS) ANOVA revealed a significant “Group” $\times$ “Time” interaction for the positive affect subscale of the PANAS ($F_{(2,48)} = 3.60$, $P < 0.05$). Post-hoc *t* tests showed a significant decrease of positive affect following right active ($P < 0.05$) and sham cTBS ($P < 0.05$) but not following left active stimulation (Fig. 2). This decrease was also reflected by a significant main effect of “Time” ($F_{(1,48)} = 10.42$, $P < 0.05$). Contrary, the same analysis of negative affect and state anxiety resulted in significant main effects of “Time” ($F_{(1,48)} = 5.13$, $P < 0.05$ for negative affect; $F_{(1,48)} = 7.69$, $P < 0.01$ for state anxiety), indicating decreases following TBS over all groups. No further interaction or group effects were observed. Analysis of state anger revealed no significant effects.

Behavioral Data

At baseline, paired-sample *t* tests showed an emotional Stroop effect for error rates ($t_{(49)} = 8.64$, $P < 0.001$) but not reaction times. Subjects made significantly more errors during the presentation of anxiety compared to neutral words.

Figure 1.

Position of probes and channels mapped onto an MR scan of one single subject. Red dots represent light emitters and blue dots represent light detectors. Between every emitter and detector O_2Hb levels were measured by the respective channel. Green channel numbers correspond to ROI channels covering the DLPFC.

Figure 2.

Changes in positive affect (PANAS) over the course of the experiment. Error bars depict the standard error of the mean.

For the analysis of baseline compared to post measures, a significant effect of “Condition” ($F_{(1,47)} = 129.60, P < 0.001$) was again observed for error rates following cTBS in a three-factorial “Time” $\times$ “Condition” $\times$ “Group” repeated measures ANOVA. Subjects made more errors indexing anxiety compared to neutral words. In contrast, a trend for “Condition” was also found for reaction time measures ($F_{(1,47)} = 3.39, P < 0.10$) indicating that subjects tended to respond faster to anxiety words. Significant main effects for reaction times were also found for the factors “Group” ($F_{(2,47)} = 3.37, P < 0.05$) and “Time” ($F_{(1,47)} = 5.23, P < 0.05$). Subjects responded generally faster during the baseline measurement and subjects in the control group were significantly faster than those in the left-hemispheric cTBS group ($P < 0.05$). However, no interaction was observed.

Figure 3.

Activation maps show increased levels of O_2Hb during baseline measures. Maps were superimposed on a standardized brain template.

FNIRS

One-sample *t* tests against zero over all subjects showed widespread increases in prefrontal oxygenation for both conditions at baseline. During the presentation of neutral and anxiety words significant O₂Hb increases were found in 41 and 42 channels, respectively. Particularly, bilateral dorsolateral, bilateral anterior orbitofrontal, and right ventrolateral areas were recruited during the task (Fig. 3). All ROI channels were significantly activated ($P < 0.001$). No significant oxygenation patterns were observed for the contrast between both conditions.

A “Condition” $\times$ “Group” ANOVA for repeated measures revealed no significant interaction or main effect of condition prior to stimulation. However, a significant group difference was found ($F_{(2,35)} = 3.78$, $P < 0.05$). In the sham stimulation group subjects showed higher levels of O₂Hb compared to the active stimulation groups (sham $>$ right: $P = 0.05$; sham $>$ left: $P = 0.10$). Therefore, for post measures, a “Time” $\times$ “Condition” ANOVA for repeated measures was calculated for each group separately. No significant main or interaction effects were found for the sham or right active cTBS groups. However, for the left active cTBS group a significant main effect of “Time” was observed ($F_{(1,10)} = 7.30$, $P < 0.05$), indicating markedly reduced O₂Hb levels following cTBS (Fig. 4).

DISCUSSION

The results of the present study illustrate that cTBS applied to the left DLPFC had a measurable inhibitory effect on bilateral hemodynamic activity. Moreover, positive mood was significantly affected in this group. However, contrary to our hypotheses, no behavioral effects were found following PFC inhibition.

The current results are in line with the only previous fNIRS study investigating TBS effects on sensory, motor, and premotor cortices [Mochizuki et al., 2007]. Similar to our findings, the authors found attenuating cTBS effects on O₂Hb in areas contralateral to the site of stimulation (no measures were recorded for ipsilateral stimulation sites). Our results are also comparable to earlier findings of a suppressed BOLD signal response following stimulation of the frontal eye field in an fMRI study by Hubl et al. [2008]. Although comparability between the fMRI BOLD and fNIRS O₂Hb response is limited, since the BOLD signal seems to be more related to HHb signal changes [for a review see Steinbrink et al., 2006], cTBS has apparently significant influence on the hemodynamic response.

Though left active cTBS had an attenuating effect on hemodynamic activity, we observed no inhibition following right active stimulation. A similar asymmetric inhibitory impact of cTBS on the DLPFC was also reported in a PET study by Ko et al. [2008]. Modulations of striatal dopaminergic activity and behavioral performance during a set-shifting task were only found following cTBS over the left but

not right DLPFC. This asymmetric effect might have been due to left-hemispheric dominance since all subjects in this study and the current experiment were right-handed. Another explanation is that both studies used completely different methodological approaches and results might have been caused by different underlying neural and metabolic processes. Finally, without knowledge about subjects’ individual anatomy we cannot ascertain whether the appropriate region was sufficiently targeted during stimulation. Regarding the small sample size, it is possible that cTBS affected regions other than the right DLPFC. Contradicting this hypothesis is the observation that F3 and F4 correspond to the medial frontal gyrus and cover parts of the left and right DLPFC, respectively [Herwig et al., 2003]. Even if cTBS might have been applied to a neighboring brain region, effects on this area were measured by fNIRS since the calculated ROI also covered F3 and F4. A neuronavigation system might, however, be of profound benefit to further studies addressing these questions.

The finding of a bilateral reduction of O₂Hb is not surprising taking the inter-hemispheric connections into account and also earlier observations of a delayed but similar effect of TMS on the contralateral site of stimulation [Ilmoniemi et al., 1997].

Apart from the neurovascular effect, results show a significant positive impact of left DLPFC inhibition on mood. Positive affect markedly decreased during the course of the experiment in the right active and sham cTBS groups. This was not unexpected and probably due to fatigue and the long-lasting experimental procedure. Contrary, no such decrease was present in the left-hemispheric TBS group which showed stable levels on this scale. Considering the therapeutic potential of rTMS for mood disorders, this observation is interesting but on the other hand questionable since mood enhancing effects were primarily found for either excitatory high-frequency rTMS over the

Figure 4.

Changes in DLPFC O₂Hb levels following active and sham cTBS. Error bars depict the standard error of the mean O₂Hb signal.

left PFC or inhibitory low-frequency rTMS over the right PFC [Gershon et al., 2003; Loo and Mitchell, 2005]. On the other hand, even high-frequency rTMS might have beneficial interfering effects on neuronal activity.

Contrasting our hypothesis, we could not support findings emphasizing an important functional role of the PFC for top-down control during the processing of fear-relevant stimuli although subjects made more errors in response to anxiety words. Anxiety compared to neutral words led to no additional recruitment of the DLPFC and inhibitory TBS caused no behavioral effects. One possible explanation for this finding might be that subjects successfully compensated for the interfering cTBS effects. It is likely that other cortical or subcortical areas were recruited to compensate for the lack of prefrontal control. Furthermore, the precise networks involved during the task could not be tracked by fNIRS due to limited spatial resolution. As a result, changes in the amygdala or anterior cingulate cortex (ACC) were not monitored. Both structures have been assumed to play a role during the emotional Stroop task although even PET and fMRI findings are inconsistent regarding their involvement [Compton et al., 2003; George et al., 1993; Isenberg et al., 1999; Whalen et al., 1998].

Furthermore, stimulus material displayed mainly symptoms of acute fear and anxiety thereby being particularly relevant for anxiety sensitive subjects. But regarding psychometric data, the present sample was little anxious at all. The sample's ASI scores were four points below the norm scores according to Peterson and Reiss [1992]. One can assume that the words were striking enough to draw attention away from the task but did not substantially activate the fear-network, at least in healthy subjects. In addition, evidence exists that both anxiety sensitivity and trait anxiety can affect the performance of emotional Stroop tasks [Richards et al., 1992; Stewart et al., 1998].

CONCLUSION

To conclude, we showed that hemodynamic activity was significantly reduced following cTBS over the left but not right DLPFC. This attenuation was present at both the actual site of stimulation and the contralateral brain region. However, no behavioral effects were observed following PFC inhibition. Future studies might preferentially focus on subjects with elevated or pathologically enhanced anxiety levels in order to challenge the regulatory top-down function of the PFC.

To the best of our knowledge, the current study showed for the first time that also prefrontal cTBS led to significant decreases in the fNIRS signal.

REFERENCES

- Alpers GW, Pauli P (2001): Angstsensitivitäts-Index. Wuerzburg: Julius-Maximilians-Universität.
- Bar-Haim Y, Lamy D, Pergamin L, Bakermans-Kranenburg MJ, Ijzendoorn MH (2007): Threat-related attentional bias in anxious and nonanxious individuals: A meta-analytic study. *Psychol Bull* 133:1–24.
- Barker AT, Jalinous R, Freeston IL (1985): Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1:1106–1107.
- Berkowitz RL, Coplan JD, Reddy DP, Gorman JM (2007): The human dimension: How the prefrontal cortex modulates the subcortical fear response. *Rev Neurosci* 18:191–207.
- Cárdenas-Morales L, Nowak D, Kammer T, Wolf R, Schönfeldt-Lecuona C (2010): Mechanisms and applications of theta-burst rTMS on the human motor cortex. *Brain Topogr* 22:294–306.
- Compton RJ, Banich MT, Mohanty A, Miham MP, Herrington J, Miller GA, Scalf PE, Webb A, Heller W (2003): Paying attention to emotion: An fMRI investigation of cognitive and emotional Stroop tasks. *Cogn Affect Behav Neurosci* 3:81–96.
- d'Alfonso AAL, van Honk J, Hermans E, Postma A, de Haan EHF (2000): Laterality effects in selective attention to threat after repetitive transcranial magnetic stimulation at the prefrontal cortex in female subjects. *Neurosci Lett* 280:195–198.
- Dearing J, George MS, Greenberg BD, Wassermann EM, Schlaepfer TE, Murphy DL, Hallett M, Post RM (1997): Mood effects of prefrontal repetitive high frequency transcranial magnetic stimulation (rTMS) in healthy volunteers. *CNS Spectr* 2:53–68.
- Dresler T, Ehlig A-C, Plichta MM, Richter MM, Jabs B, Lesch KP, Fallgatter AJ (2009a): Panic disorder and a possible treatment approach by means of high-frequency rTMS: A case report. *World J Biol Psychiatry* 10:991–997.
- Dresler T, Mériaux K, Heekeren H, van der Meer E (2009b): Emotional Stroop task: Effect of word arousal and subject anxiety on emotional interference. *Psychol Res* 73:364–371.
- First MB, Spitzer RL, Gibbon M, Williams JBW (2002): Structured Clinical Interview For DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P). New York, NY: Biometrics Research, New York State Psychiatric Institute.
- George MS, Ketter TA, Parekh PI, Rosinsky N, Ring H, Casey BJ, Trimble MR, Horwitz B, Herscovitch P, Post RM (1993): Regional brain activity when selecting a response despite interference: An H₂¹⁵O PET study of the Stroop and an emotional Stroop. *Hum Brain Mapp* 1:194–209.
- Gershon AA, Dannon PN, Grunhaus L (2003): Transcranial magnetic stimulation in the treatment of depression. *Am J Psychiatry* 160:835–845.
- Grossheinrich N, Rau A, Pogarell O, Hennig-Fast K, Reinl M, Karch S, Dieler A, Leicht G, Mulert C, Sterr A, et al. (2009): Theta burst stimulation of the prefrontal cortex: Safety and impact on cognition, mood, and resting electroencephalogram. *Biol Psychiatry* 65:778–784.
- Hallett M (2000): Transcranial magnetic stimulation and the human brain. *Nature* 406:147–150.
- Hariri AR, Bookheimer SY, Mazziotta JC (2000): Modulating emotional responses: Effects of a neocortical network on the limbic system. *Neuroreport* 11:43–48.
- Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR (2003): Neocortical modulation of the amygdala response to fearful stimuli. *Biol Psychiatry* 53:494–501.
- Herwig U, Satrapi P, Schönfeldt-Lecuona C (2003): Using the international 10–20 eeg system for positioning of transcranial magnetic stimulation. *Brain Topogr* 16:95–99.
- Hess G, Donoghue JP (1996): Long-term potentiation and long-term depression of horizontal connections in rat motor cortex. *Acta Neurobiol Exp (Wars)* 56:397–405.

- Hoshi Y, Kobayashi N, Tamura M (2001): Interpretation of near-infrared spectroscopy signals: A study with a newly developed perfused rat brain model. *J Appl Physiol* 90:1657–1662.
- Huang Y-Z, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC (2005): Theta burst stimulation of the human motor cortex. *Neuron* 45:201–206.
- Hubl D, Nyffeler T, Wurtz P, Chaves S, Pflugshaupt T, Lüthi M, von Wartburg R, Wiest R, Dierks T, Strik WK, et al. (2008): Time course of blood oxygenation level-dependent signal response after theta burst transcranial magnetic stimulation of the frontal eye field. *Neuroscience* 151:921–928.
- Hyman JM, Wyble BP, Goyal V, Rossi CA, Hasselmo ME (2003): Stimulation in hippocampal region CA1 in behaving rats yields long-term potentiation when delivered to the peak of theta and long-term depression when delivered to the trough. *J Neurosci* 23:11725–11731.
- Ilmoniemi RJ, Virtanen J, Ruohonen J, Karhu J, Aronen HJ, Näätänen R, Katila T (1997): Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *Neuroreport* 8:3537–3540.
- Isenberg N, Silbersweig D, Engelien A, Emmerich S, Malavade K, Beattie B, Leon AC, Stern E (1999): Linguistic threat activates the human amygdala. *Proc Natl Acad Sci USA* 96:10456–10459.
- Jasper HH (1958): The ten-twenty electrode system of the international federation. *Electroencephalogr Clin Neurophysiol* 10:370–375.
- Jöbsis FF (1977): Non-invasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* 198:1264–1267.
- Kalisch R, Wiech K, Herrmann K, Dolan RJ (2006): Neural correlates of self-distraction from anxiety and a process model of cognitive emotion regulation. *J Cogn Neurosci* 18:1266–1276.
- Knecht S, Flöel A, Dräger B, Breitenstein C, Sommer J, Henningsen H, Ringelstein EB, Pascual-Leone A (2002): Degree of language lateralization determines susceptibility to unilateral brain lesions. *Nat Neurosci* 5:695–699.
- Ko JH, Monchi O, Pitto A, Bloomfield P, Houle S, Strafella AP (2008): Theta burst stimulation-induced inhibition of dorsolateral prefrontal cortex reveals hemispheric asymmetry in striatal dopamine release during a set-shifting task—a TMS-¹¹C-raclopride PET study. *Eur J Neurosci* 28:2147–2155.
- Krohne HW, Egloff B, Kohlmann CW, Tausch A (1996): Investigations with a German version of the positive and negative affect schedule (PANAS). *Diagnostica* 42:139–156.
- Laux L, Glanzmann P, Schaffner P, Spielberger CD (1981): *Das State-Trait-Angstinventar (STAI)*. Weinheim: Beltz.
- Loo CK, Mitchell PB (2005): A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy. *J Affect Disord* 88:255–267.
- Lundh LG, Wikström J, Westerlund J, Öst LG (1999): Preattentive bias for emotional information in panic disorder with agoraphobia. *J Abnorm Psychol* 108:222–232.
- Meyer BU, Diehl RR, Steinmetz H, Britton TC, Benecke R (1991): Magnetic stimuli applied over motor cortex and visual cortex: Influence of coil position and field polarity on motor responses, phosphenes, and eye movements. *Electroencephalogr Clin Neurophysiol Suppl* 43:121–134.
- Mochizuki H, Furubayashi T, Hanajima R, Terao Y, Mizuno Y, Okabe S, Ugawa Y (2007): Hemoglobin concentration changes in the contralateral hemisphere during and after theta burst stimulation of the human sensorimotor cortices. *Exp Brain Res* 180:667–675.
- Obrig H, Villringer A (2003): Beyond the visible—Imaging the human brain with light. *J Cereb Blood Flow Metab* 23:1–18.
- Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JDE, Gross JJ (2004): For better or for worse: Neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage* 23:483–499.
- Pascual-Leone A, Gates JR, Dhuna A (1991): Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. *Neurology* 41:697–702.
- Peterson RA, Reiss S (1992): *Anxiety Sensitivity Index Manual*. Worthington: International Diagnostic Systems.
- Plichta MM, Herrmann MJ, Baehne CG, Ehlis A-C, Richter MM, Pauli P, Fallgatter AJ (2006): Event-related functional near-infrared spectroscopy (fNIRS): Are the measurements reliable? *Neuroimage* 31:116–124.
- Plichta MM, Heinzel S, Ehlis A-C, Pauli P, Fallgatter AJ (2007): Model-based analysis of rapid event-related functional near-infrared spectroscopy (fNIRS) data: A parametric validation study. *Neuroimage* 35:625–634.
- Richards A, French CC, Johnson W, Naparstek J, Williams J (1992): Effects of mood manipulation and anxiety on performance of an emotional Stroop task. *Br J Psychol* 83:479–491.
- Schecklmann M, Ehlis AC, Plichta MM, Fallgatter AJ (2010): Influence of muscle activity on brain oxygenation during verbal fluency assessed with functional near-infrared spectroscopy. *Neuroscience* 171:434–442.
- Schwenkmezger P, Hodapp V, Spielberger CD (1992): *Das State-Trait-Ärgerausdrucks-Inventar STAXI Handbuch*. Bern: Hans Huber.
- Steinbrink J, Villringer A, Kempf F, Haux D, Boden S, Obrig H (2006): Illuminating the bold signal: Combined fMRI-fNIRS studies. *Magn Reson Imaging* 24:495–505.
- Stewart SH, Conrod PJ, Gignac ML, Pihl RO (1998): Selective processing biases in anxiety sensitive men and women. *Cogn Emot* 12:105–133.
- Strangman G, Boas DA, Sutton JP (2002a): Non-invasive neuroimaging using near-infrared light. *Biol Psychiatry* 52:679–693.
- Strangman G, Culver JP, Thompson JH, Boas DA (2002b): A quantitative comparison of simultaneous bold fMRI and NIRS recordings during functional brain activation. *Neuroimage* 17:719–731.
- Thomas SJ, Johnstone SJ, Gonsalvez CJ (2007): Event-related potentials during an emotional Stroop task. *Int J Psychophysiol* 63:221–231.
- Whalen PJ, Bush G, McNally RJ, Wilhelm S, McInerney SC, Jenike MA, Rauch SL (1998): The emotional counting Stroop paradigm: A functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biol Psychiatry* 44:1219–1228.
- Williams JMG, Mathews A, MacLeod C (1996): The emotional Stroop task and psychopathology. *Psychol Bull* 120:3–24.