Unilateral Left Prefrontal Transcranial Magnetic Stimulation (TMS) Produces Intensity-Dependent Bilateral Effects as Measured by Interleaved BOLD fMRI

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Transcranial magnetic stimulation (TMS) administered over the prefrontal cortex has been shown to subtly influence neuropsychological tasks, and has antidepressant effects when applied daily for several weeks. Prefrontal TMS does not, however, produce an immediate easily observable effect, making it hard to determine if one has stimulated the cortex. Most prefrontal TMS studies have stimulated using intensity relative to the more easily determined motor threshold (MT) over motor cortex.

Five healthy adults were studied in a 1.5 T MRI scanner during short trains of 1 Hz TMS delivered with a figure eight MR compatible TMS coil followed by rest epochs. In a randomized manner, left prefrontal TMS was delivered at 80%, 100% and 120% of MT interleaved with BOLD fMRI acquisition.

Compared to rest, all TMS epochs activated auditory cortex, with 80% MT having no other areas of significant activation. 100% MT showed contralateral activation and 120% MT showed bilateral prefrontal activation. Higher intensity TMS, compared to lower, in general produced more activity both under the coil and contralaterally.

Higher prefrontal TMS stimulation intensity produces greater local and contralateral activation. Importantly, unilateral prefrontal TMS produces bilateral effects, and TMS at 80% MT produces only minimal prefrontal cortex activation. Biol Psychiatry 2001;50:712–720 © *2001 Society of Biological Psychiatry*

Key Words: TMS, prefrontal, fMRI, connectivity

Introduction

In recent years, transcranial magnetic stimulation (TMS) has emerged as a research and perhaps therapeutic tool (George et al 1999a; George and Belmaker 2000). Transcranial magnetic stimulation noninvasively induces electrical currents in cortical neurons, and thus can be used to probe brain–behavior relationships in awake alert adults. This "electrodeless electrical stimulation," as TMS is sometimes called, is made possible by placing a small coil of wire on the scalp and passing a very powerful current through it (Barker et al 1985). This then produces a brief but powerful magnetic field that passes unimpeded through the tissues of the head. The magnetic field, in turn, induces a much weaker electrical current in the brain, causing focal brain stimulation. The magnetic field changes decline exponentially with distance away from the coil. Even though conventional TMS can directly activate only cortical neurons, it also affects brain regions at some distance from the stimulation site, most likely through transsynaptic connections (Bohning et al 1998; Kimbrell et al 1997; Paus et al 1997; Teneback et al 1999). Transcranial magnetic stimulation at different intensities, frequencies, locations and with different coil orientations likely stimulates different groups of neurons, and has varying behavioral effects (Hallett 2000; Ziemann and Hallett 2000). As a research tool, TMS has been applied in studies of brain mapping, motor cortex neurophysiology (Ziemann and Hallett 2000), and to understand language (Epstein et al 1996) and vision (Amassian et al 1989). It has also been investigated as a potential treatment in a range of neuropsychiatric disorders such as depression (Berman et al 2000; Conca et al 1996; Figiel et al 1998; George et al 1995b, 1997; Grisaru et al 1994; Grunhaus et al 2000; Hoflich et al 1993; Klein et al 1999b; Kolbinger et al 1995; Lieberman, 1998; Loo et al 1999; Padberg et al 1998; Triggs et al 1999), mania (Grisaru et al 1998b), schizophrenia (Berman et al 2000; Davey et al 1997;

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Received March 12, 2001; revised May 7, 2001; accepted May 16, 2001.

0006-3223/01/$20.00
PII S0006-3223(01)01199-4

Hoffman et al 1998; Klein et al 1999a; Nahas et al 1999; Puri et al 1996), Obsessive Compulsive Disorder (OCD) (Greenberg et al 1997), anxiety (Grisaru et al 1998a), Tourette syndrome (George et al 2000b; Ziemann et al 1997), and Parkinson's disease (Mally and Stone 1999). Such applications have ranged from a single hour-long session to daily applications for several weeks. Depending on the paradigm studied, prefrontal TMS has been reported to induce changes in mood (George et al 1996; Martin et al 1997; Mosimann et al 2000; Pascual-Leone et al 1996), working memory (Jahanshahi et al 1998; Grafman and Wassermann, 1999; Pascual-Leone et al 1993), sleep (Cohrs et al 1998; Stadler et al 1995), peripheral neuroendocrine measures (George et al 1996; Martin et al 1997; Pridmore 1999; Szuba et al 1999) and anxiety or obsessive thinking (Greenberg et al 1995).

Despite this growing interest in using TMS as a research tool at a systems or circuit level, and its potential for therapeutic use, researchers are largely uninformed about its neurobiologic effects, particularly as a function of the use parameters such as intensity, frequency and dose. Animal work has demonstrated changes in monoamines (Ben-Sachar et al 1997; Freedman et al 1999), glutamate (Kole et al 1999) and c-fos gene expression in rat's brain (Ji et al 1998) and induced electrical currents in primates (Lisanby et al 1998a, 1998b). Much of the basic information about the neurobiologic effects of TMS in humans comes from electrophysiologic studies over motor (Greenberg et al 1998; Wassermann et al 1998; Ziemann and Hallett 2000) or visual cortex (Amassian et al 1993), where one can readily measure an external behavioral effect (motor evoked potentials or phosphenes); however, this body of information has limited value in understanding TMS effects at other sites, such as prefrontal cortex, where there is no electrophysiological marker like a motor evoked potential (MEP) and where the cytoarchitecture is known to be different from primary motor or sensory cortex. A few radio-tracer-based (PET and SPECT) neuroimaging studies (Kimbrell et al 1997, 1999; Paus et al 1997; Speer et al 2000; Teneback et al 1999, Paus et al 2001) have begun to shed light on prefrontal TMS mechanisms of action. They have shown that it has local effects compared to sham stimulation (Teneback et al 1999). They have also described correlational changes in brain activity in other regions; however, they have not specifically examined the role of the intensity of stimulation or whether there are bilateral prefrontal and limbic effects of unilateral prefrontal stimulation.

Recently, our laboratory has demonstrated the feasibility of interleaving TMS with blood oxygen level dependent (BOLD) fMRI, allowing one to image, with good spatial and temporal resolution, the effect of TMS on regional cerebral blood flow (rCBF) (Bohning et al 1998, 1999, 2000; Shastri et al 1999). Our initial studies with interleaved TMS/fMRI were performed over motor cortex because of the ready ability to position the TMS coil and reliably observe a peripheral effect (thumb movement). Thus, over motor cortex, one can insure that the TMS coil is correctly positioned to access the motor cortex at an angle and intensity sufficient to produce contralateral external movement. Using this behavioral approach to TMS coil placement (e.g., seeing the thumb move) (George and Bohning 2000), we have demonstrated rCBF changes as a function of different intensities (Bohning et al 1999) and across a range of stimuli (Bohning et al 2000). Further, we have shown that TMS at MT and 1 Hz has local effects that resemble the normal physiology of volitional activity (Bohning et al 2000).

In clinical settings involving TMS over the prefrontal cortex, most studies have dosed the TMS intensity output relative to the motor threshold (MT). Because of differences between prefrontal and motor cortex in distance from skull and in intrinsic cytoarchitecture, we questioned how and whether the dose needed to activate the prefrontal cortex related to the motor cortex determined motor threshold. We hypothesized that prefrontal stimulation at a higher intensity would demonstrate more local and remote activation; and that unilateral TMS would be associated with bilateral hemispheric brain activity changes.

Methods and Materials

General Experimental Design

We enrolled seven healthy adults who signed a written informed consent approved by the Institutional Review Board of the Medical University of South Carolina. Only five subjects (two women, mean age 34 ± 6, all right-handed) had data acquired in a manner that allowed for group statements (two had datasets that could not be transformed into a common brain space due to a small volume of imaged brain, which lacked key landmarks needed for spatial normalization). A custom built modified nonferromagnetic Dantec figure eight TMS coil (Dantec Medical A/S) was specially mounted within a 1.5 T Picker clinical MR scanner (Picker International, Inc., Cleveland, OH). The TMS coil was attached to RF filters and interleaved with fMRI acquisition using an independent computer control (PowerMac 7100/80AV; Apple Computer Inc., Cupertino, CA, USA) (for more information, see Shastri et al 1999). The same TMS coil was initially used to determine each subject's motor threshold (MT) according to the method of limits (Pridmore et al 1998). Motor threshold for right thumb was determined by initially defining the optimal area over the left motor cortex to induce a thumb movement. The stimulation intensity was gradually decreased until a movement (slight twitch) was no longer observed. Motor threshold for that individual was thus the intensity setting on the Dantec (in 5% increments) that produced a visible twitch in the contralateral thumb at least five out ten stimulations. The site of left prefrontal stimulation was determined and marked

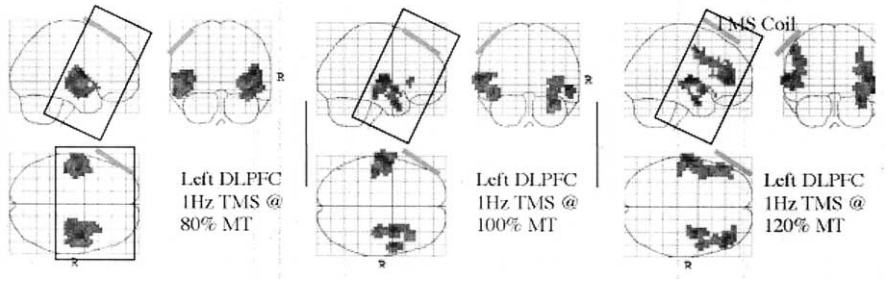

Figure 1. These are 3-dimensional "look-through" projections of statistical parametric maps of the brain regions that were significantly active when comparing separately 1 Hz TMS epoch (at three different intensities of stimulation) to rest epoch immediately before TMS (height threshold $p < .001$ and extent threshold $p = .05$). Note the position of the TMS coil and the oblique area imaged. All three different stimulation intensities show activation of the temporal cortex. Also note the intensity-dependent activation at the site of stimulation (only present at 120% MT), contralateral activations of the prefrontal lobe (asymmetric activation at 100% MT) and bilateral activations of prefrontal lobes (at 120% MT).

5 cm forward in a parasagittal line from the optimal area for MT. Once subjects were lying on the gantry of the scanner, they wore earphones and earplugs. The TMS coil was rigidly mounted in the MR head coil and positioned over the left prefrontal cortex in the same coil orientation used for determining MT over motor cortex. Vitamin E capsules were placed at the ends of the TMS coil, behind it and at its center to help locate the TMS coil in the structural images. The head was then stabilized with foam padded inflatable restraints.

Acquisition

A T-1 weighted scan was obtained with 12 oblique slices (slice thickness = 5 mm, slice gap = 1.5 mm) centered between the prefrontal cortex anteriorly and the auditory cortex posteriorly with the thalamus in between (voxel size $2 \times 2 \times 5$ mm). These allowed later co-registration of functional data with structural images acquired in the same plane and then transformation into Tailarach space. The relative timing of EPI acquisitions and TMS stimulation was controlled using a PowerMac 7100/80AV (Apple Computer, Inc., Cupertino, CA, USA) with a general purpose input/output (I/O) board (NB-MIO-16 $\times$ H) and LabView software package (National Instruments Corp., Austin, TX, USA). The EPI acquisitions were performed normally in a free running steady-state mode, whereas the PowerMac counted the RF synchronization pulses generated by the scanner for each acquisition. Blood oxygen level dependent single-shot EPI-fMRI images were acquired in the same plane (12 slices, 111×10^{-8} matrix, FOV + 270 mm, TE = 40.0 msec, TR = 3 sec, slice thickness = 5 mm, slice gap = 1.5 mm, with frequency selective fat saturation).

Stimulation

At the appropriate counts, the PowerMac generated a 5V transistor transistor logic (TTL) pulse through the I/O board to trigger the Dantec MagPro via its external triggering feature (Shastri et al 1999). The entire TMS/fMRI sequence (22 min, 3 sec), consisted of seven cycles. Each cycle consisted of nine 21-sec subcycles (six rest and three stimulation condition). During the stimulation condition subcycles, the TMS was triggered 100 msec after every fourth image acquisition to produce a TMS stimulation rate of 1 Hz. Twenty-one second rest epochs preceded and followed short trains (21 pulses) of 1 Hz TMS (repeated over seven cycles). Transcranial magnetic stimulation was delivered (in a randomized manner) at 80%, 100% and 120% of MT. Two minutes before the beginning of the functional imaging and all throughout it, subjects performed a continuous performance task by listening through headphones (with earplugs in as well) to three different and randomized tones (low, mid and high pitch) presented at one tone per second with the instruction to lift their index finger at the sound of the highest pitch.

Image Analysis

All images were translated into ANALYZE format (CNSoftware Ltd., West Sussex, UK) and transferred to Sun SPARCstations for further analyses with MEDx 3.0 (Sensor Systems, Inc. Sterling, VA, USA). Images were initially checked for motion across the whole acquisition, and all scans met our requirement of movement less then 3 mm across x, y and z dimensions. Because the original images were acquired oblique and did not cover the whole brain, they were re-sliced in coronal planes to facilitate transformation into Talairach space. Images were then spatially and intensity normalized, smoothed ($8 \times 8 \times 8$ mm) and converted into Talairach space. The anterior commissure was identified in all scans and had to fall in either the sixth or seventh initial slice, otherwise a mean image could not be obtained. Two of the seven studies did not meet this criterion and were excluded for final analysis (their oblique data were acquired too far posterior for this form of Talairach transformation). A mean image of the five subjects with usable data were therefore used for group statistics.

Comparisons

Paired *t* tests were performed between images "during TMS" at different intensities (80%, 100%, 120% MT) and the immedi-

Table 1. Talairach Coordinates of Significant Regions

Different SPM analyses	Tailarach coordinates x, y, z	*Z* value	Region of activation
TMS compared to rest epoch before stimulation: (ht $p < .001$, extent $p < .05$)			
80% MT			
	52, −8, 16	6.05	Right post central gyrus (extending into auditory cortex, middle temporal gyrus, superior temporal gyrus)
	−40, −12, 12	5.27	Left insula (extending into auditory superior temporal gyrus)
100% MT			
	−60, −20, 12	6.31	Left superior temporal gyrus (extending into Brodmann Area (BA) 41, 42, inferior longitudinal fasiculus)
	40, 0, −20	5.37	Right auditory (middle temporal gyrus) extending into insula
	60, 0, −4	5.01	Right superior temporal gyrus (BA 22)
	40, 20, 8	3.65	Right insula (extending into inferior frontal gyrus)
120% MT			
	−56, −12, 12	6.2	BA 42 (extending into superior temporal gyrus)
	48, 36, 12	5.57	Right inferior frontal gyrus, BA 46 (extending into GFM BA 9, GFM BA 46)
	40, −4, −20	5.35	Right middle temporal gyrus, BA 21 (extending into superior temporal gyrus, insula)
	−48, −4, 48	4.83	Left precentral gyrus, BA 4 (extending into Gfi BA 46, GFm BA 9)
	56, 0, −4	4.41	Right superior temporal gyrus BA 22 (extending into GFI BA 47, GTS BA 22)
	36, −4, 40	3.97	Right precentral gyrus, BA 6
TMS comparisons between different intensities: (ht $p < .01$, extent $p < .05$)			
120% MT minus 100% MT			
	44, 44, −12	4.7	Right inferior frontal gyrus
100% MT minus 80% MT			
	none met threshold	—	—
120% MT minus 80% MT			
	−16, 4, 44	3.9	Left cingulate gyrus
	−44, 24, 16	3.67	Left inferior frontal gyrus (extending into middle frontal gyrus)

Z values, Talairach coordinates (x, y, z in mm) and locations of center of significance for all results, $p < .001$. All clusters have a significance of extent of $p < .05$.

ately preceding rest epoch to generate maps of significant pixels at threshold $p < .001$ and extent $p < .05$ using SPM 96 embedded within MEDx 3.0. We also directly compared images during TMS across the different intensities (120% − 100% MT and 100% − 80% MT).

Results

Safety and Tolerability

None of the subjects reported adverse side effects from the stimulation. All subjects reported being able to attend to, and perform, the CPT during the TMS epochs.

For TMS compared to the rest epoch before stimulation, see Figure 1 and Table 1.

There was significant activation only in the bilateral midtemporal lobes (auditory cortex) within the restricted field of view, with right middle temporal gyrus extending into the right insula (80% MT minus rest).

There was significant activation in the bilateral midtemporal lobes (auditory cortex) and right insula. In addition, there was small contralateral (right) prefrontal activation. Of particular note, brain activity was not significantly increased from rest at the site of stimulation immediately underneath the coil (100% MT minus rest).

There was significant activation in the bilateral midtemporal lobes (auditory cortex) extending to the right insula. Further, there was extensive bilateral prefrontal activation, including regions directly under the coil [right Brodmann Area (BA) 46, left BA 4 (somatosensory) extending into BA 46 and 9] [120% MT minus rest (see Figure 2)].

For TMS comparisons during TMS between different intensities, see Figure 3).

There was increased brain activity in the right orbitofrontal cortex with 120% MT stimulation compared to stimulation at MT (TMS delivered at 120% MT compared to MT; $p < .01$).

There were no significant pixels for the comparison TMS delivered at MT compared to 80% MT

There was increased brain activity with the higher intensity in the left cingulate gyrus and the left prefrontal cortex (at the site of stimulation) (TMS delivered at 120% MT compared to 80% MT).

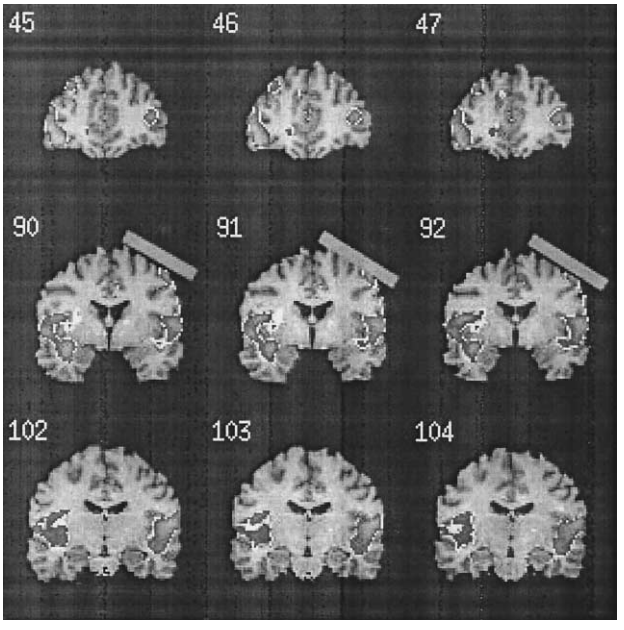

Figure 2. 1 Hz left prefrontal TMS (bar) at 120% MT causes changes in the left DLPFC (site of stimulation), right orbitofrontal, bilateral auditory cortex and right anterior temporal pole.

Discussion

This study used the new technique of interleaved TMS/fMRI to test the role of the stimulation intensity over the prefrontal cortex, where the immediate effects of TMS are not as easily observed as over motor cortex. Given the know connections of prefrontal cortex with ipsi and contralateral brain regions (Schwartz and Goldman-Rakic 1984), it also examined whether unilateral stimulation had unilateral (or bilateral) effects. Although this first prefrontal study with this interleaved TMS/fMRI technique has several limitations, there are four main results of prefrontal stimulation at 1 Hz in healthy adults.

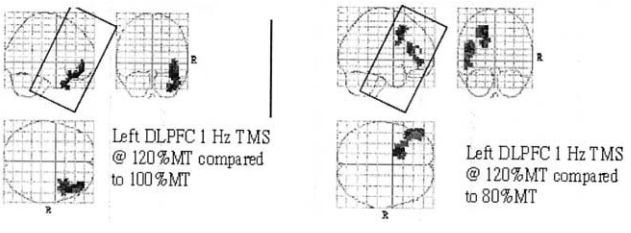

Figure 3. These are 3-dimensional "look-through" projections of SPM with brain regions that were significantly active when comparing separately 1 Hz TMS epochs at (**A**) 120% MT to 100% MT, and at (**B**) 120% MT to 80% MT (height threshold $p < .001$ and extent threshold $p = .05$). With increased intensity of stimulation, note the (**A**) controlateral orbitofrontal activation, and (**B**) site of stimulation underneath the coil. Note that the comparison of 100% MT to 80% MT yielded no statistically significant activation at the above threshold.

- In general, *higher intensity* stimulation produced *greater* local and contralateral activation.
- Unilateral TMS applied over the prefrontal cortex (left) had *bilateral* effects.
- There were greater effects seen in the right (non-stimulated) cortex than the stimulated left side at all intensities.
- 80% MT prefrontal stimulation at 1 Hz for 20 sec failed to produce significant prefrontal changes compared to rest.

Several limitations need to be kept in mind when interpreting these data. The interaction between CPT performance and the TMS on blood flow cannot be ruled out in our study. Before designing the study, we had contemplated not using such a task but we were concerned that subjects would engage in different cognitive processes. We chose to have a common simple (raise finger at the highest tone) attentional task to all subjects. We did not measure performance on CPT during imaging although none of the subjects reported difficulty in executing this task while receiving TMS.

Our early studies have shown that there may be a potential reduction in signal immediately below the coil (Bohning et al 1998). This may render a confound in making statements about unilateral versus contralateral effects, although this should not affect statements about brain activity changes with different intensities as this reduction would be uniform at a given brain region across the intensities.

Due to technical limitations that we have since overcome, we were not able to image the entire brain with this interleaved study. Although this makes the study more focused in terms of hypothesized changes in specific brain regions, there are large areas of the brain that we did not image. Thus, this study does not completely address all brain activity changes as a function of prefrontal stimulation. We also are not able to determine which brain activity changes are due to the direct effects of TMS, and which might be due to nonspecific factors. For example, higher intensity TMS is more painful than lower intensity TMS (Lorberbaum and Wassermann 2000), leaving open the possibility that the orbitofrontal activation seen with higher intensity TMS could reflect not a transynaptic and transcollosal activation but a confound of higher pain at more intense doses, with pain being processed more by right hemisphere structures (Craig et al 2000; Heavner 1999). With fMRI, one can examine individual differences and there was a great deal of heterogeneity of response across subjects' individual scans. We positioned the TMS coil in a probabilistic manner, relative to the functionally defined motor cortex region for thumb movement. One aspect of the heterogeneity across subjects is likely the variability of whether this spot is over a gyrus or sulcus, or

which prefontal gyrus this landed on within subjects (for a more detailed discussion of the issues involved in positioning the TMS coil see George and Bohning 2000). Further limitations of this study were not relying on EMG for determination of MT, the lack of an asymmetric spin echo technique to reduce artifact and the limited regions imaged.

Further, because of the small sample size and the limited number of stimulation intensities (three), we were unable to directly correlate the "threshold" for prefrontal TMS activation (determined by BOLD imaging) with the motor threshold. Future studies with larger subjects may allow for the creation of such a conversion table, which would be useful for TMS researchers stimulating over prefrontal cortex. Importantly, prefrontal stimulation below MT did not produce significant rCBF changes, implying that prefrontal stimulation needs to be performed at MT or greater to reliably stimulate the brain in a way that triggers the BOLD response. Studies with paired pulse TMS have shown that stimulation with a prepulse that is less than MT can cause inhibitory effects. Thus, the failure in this study to find significantly increased rCBF at 80% MT does not imply that 80% MT has no effect. Rather, this 80% MT effect is clearly smaller in terms of the BOLD response than stimulation at higher intensities. If stimulation with 1 Hz TMS at lower intensities recruits relatively more local inhibitory neurons than does higher intensity stimulation, then there may be an inhibitory effect of 80% MT, with a smaller BOLD response. Current technology limitation prohibit from interleaving fast TMS with fMRI. It is unclear whether 20 Hz TMS at 80% MT would have similar effects on BOLD response. Due to safety concerns at that time, some of the early TMS antidepressant studies used 80% MT stimulation, with only weak therapeutic effects (George et al 1997). The weak BOLD response at 80% MT may help explain these early findings in TMS as an antidepressant.

Although this is the first study using interleaved TMS/fMRI over the DLPFC, several prefrontal stimulation studies using tracer-based imaging techniques (PET and SPECT scanning during TMS) have been published in healthy and in subjects with depression (see Table 2). Although there have been other imaging studies looking at the effect of rTMS on prefrontal cortex before and after stimulation (George et al 2000a), we have focused the discussion here to just those studies performed while prefrontal TMS was being administered. The first published combination of TMS and functional neuroimaging in real time was performed with fluorodeoxyglucose PET in a depressed patient receiving 20 Hz left DLPFC rTMS. This "during-TMS" scan at intermittent high frequency over 20 min showed marked increases in activity compared to baseline, especially over the prefrontal cortex

Table 2. Functional Imaging Studies Done during TMS Administered over the Prefrontal Cortex

Study	No. subjects	State	Modality	Intensity	Frequency	No. Pulses	Time in minutes	Control condition	Finding
George et al 1995a, 1995b	1	Depressed	FDG PET	80% MT	20 Hz	1600	20	Baseline	Increased activity in left DLPFC
Kimbrel et al 1997	15	Healthy	FDG PET	80% MT	1 Hz	1200	20	Baseline sham	Global reduction in blood flow Localized reduction in left DLPFC, cauda bilateral orbitofrontal cortex and cerebellum
George et al 1999a, 1999b	8	Healthy	SPECT	80% MT (60% MT × 2 min after injection of radiotracer)	20 Hz	2040	20	Baseline and 2-min TMS	Decreased activity in right DLPFC, bilate anterior cingulate, right anterior tempo cortex hypothalamus, thalamus (compared to baseline) Increased activity orbitofrontal cortex (Left > (compared to baseline)) Increased activity in left DLPFC (compared to 2-min TMS)
Nahas et al 2001	13	Depressed	SPECT	100% MT (60% MT × 2 min after injection of radiotracer)	5 vs. 20 Hz	2040	20	Baseline and 20 Hz vs. 5 Hz	Increased left middle frontal gyrus and right medial frontal lobe (compared to baseline) Relatively more increases of activity underneath the coil with 20 Hz compared to 5 Hz

(George et al 1995a). In contrast to this single case report in depression, Kimbrell et al (1997) found that in healthy adults, slow TMS (1 Hz) for 20 min compared to a baseline or sham condition, was associated with decreased relative metabolic activity in the left dorsolateral prefrontal cortex (the TMS site), and connected regions such as the caudate, the orbitofrontal cortex bilaterally and the cerebellum. Again in healthy adults, a study by George et al (1999b) using perfusion SPECT found relative decreases under the coil site and in the anterior cingulate and orbitofrontal cortex during 20 Hz left DLPFC rTMS compared to a control scan with sham TMS.

We recently reported the results of a perfusion SPECT study in the context of a TMS antidepressant treatment trial (with either 5 Hz or 20 Hz left DLPFC rTMS) (Nahas et al 2000). We found after 5 days of active treatment and during the fifth rTMS session, increased rCBF at the site of stimulation (left middle frontal gyrus) and the right medial frontal lobe compared to baseline. We also found relatively decreased activity at the anterior cingulate and anterior temporal poles bilaterally. When compared to each other, 20Hz rTMS had more increases in blood flow directly below the coil than did 5 Hz rTMS

In summary, limited imaging studies during prefrontal TMS have shown local and distal effects from the site of stimulation. Studies that used faster frequencies of stimulation (which may be more excitatory) and for longer durations (George 2000; Nahas 2001) have found local blood flow increases. One study with slow stimulation at 80% MT over 20 min found a reduction of brain activity underneath the coil (Kimbrell et al 1999). As this field develops, better understanding of the use parameters and imaging techniques used will help integrate the early divergent studies.

Interleaved prefrontal TMS/fMRI is feasible, and shows intensity-dependent effects both under the coil and in the contralateral cortex. The interleaved TMS/fMRI technique shows promise as a research tool for understanding the alterations in physiology with TMS. These findings of greater blood flow changes at higher stimulation intensities may help explain the trend in TMS antidepressant trials for higher stimulation intensity having a more robust antidepressant effect (Nahas et al 2001). We were also struck by the bilateral extent of TMS delivered over just one hemisphere.

This study was funded in part by foundation grants from the National Alliance for Research on Schizophrenia and Depression (NARSAD) (Independent Investigator Award to Dr. George), the Stanley Foundation (Dr. George) and the Borderline Personality Disorder Research Foundation, NIMH R01 RR14080–01 (Dr. Bohning), NINDS R01 NS40956-1 (Dr. George), equipment donations from Dantec (Medtronic) and scanner time and personnel from a developmental grant from the MUSC Center for Advanced Imaging Research (CAIR).

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