Opposite Effects of High and Low Frequency rTMS on Regional Brain Activity in Depressed Patients

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Background: High (10–20 Hz) and low frequency (1–5 Hz) repetitive transcranial magnetic stimulation (rTMS) have been explored for possible therapeutic effects in the treatment of neuropsychiatric disorders. As part of a double-blind, placebo-controlled, crossover study evaluating the antidepressant effect of daily rTMS over the left prefrontal cortex, we evaluated changes in absolute regional cerebral blood flow (rCBF) after treatment with 1- and 20-Hz rTMS. Based on preclinical data, we postulated that high frequency rTMS would increase and low frequency rTMS would decrease flow in frontal and related subcortical circuits.

Methods: Ten medication-free, adult patients with major depression (eight unipolar and two bipolar) were serially imaged using 15 O water and positron emission tomography to measure rCBF. Each patient was scanned at baseline and 72 hours after 10 daily treatments with 20-Hz rTMS and 10 daily treatments with 1 Hz rTMS given in a randomized order. TMS was administered over the left prefrontal cortex at 100% of motor threshold (MT). Significant changes in rCBF from pretreatment baseline were determined by paired t test.

Results: Twenty-hertz rTMS over the left prefrontal cortex was associated only with increases in rCBF. Significant increases in rCBF across the group of all 10 patients were located in the prefrontal cortex (L & R), the cingulate gyrus (L & R), and the left amygdala, as well as bilateral insula, basal ganglia, uncus, hippocampus, parahippocampus, thalamus, and cerebellum. In contrast, 1-Hz rTMS was associated only with decreases in rCBF. Significant decreases in flow were noted in small areas of the right prefrontal cortex, left medial temporal cortex, left basal ganglia, and left amygdala. The changes in mood following the two rTMS frequencies were inversely related (r = -.78, p < .005, n = 10) such that individuals who improved with one frequency worsened with the other.

Conclusions: These data indicate that 2 weeks of daily 20-Hz rTMS over the left prefrontal cortex at 100% MT induce persistent increases in rCBF in bilateral frontal, limbic, and paralimbic regions implicated in depression, whereas 1-Hz rTMS produces more circumscribed decreases (including in the left amygdala). These data demonstrate frequency-dependent, opposite effects of high and low frequency rTMS on local and distant regional brain activity that may have important implications for clinical therapeutics in various neuropsychiatric disorders.


Key Words: Transcranial magnetic stimulation, regional cerebral blood flow, depressed, high frequency (20 Hz), low frequency (1 Hz), positron emission tomography

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a neurologic and psychiatric research tool that has gained notable attention in recent years for its potential application as a treatment for several neuropsychiatric illnesses. It involves the use of a wire coil through which brief pulses of electrical current are passed, leading to the generation of magnetic fields that pass through the skull (Barker et al 1985, 1987). Changes in neuronal activity in the brain can thus be achieved when the coil is placed close to the scalp. A figure eight coil allows for relatively focal stimulation of the brain such that the hand or foot area of the motor cortex can be selectively activated (Cohen et al 1990; Wassermann et al 1992; Wilson et al 1993).

Transcranial magnetic stimulation results in a variety of effects depending on the target area and stimulation parameters, such as intensity and frequency. When applied over the primary motor area, single-pulse TMS evokes compound action potentials in contralateral muscles (Rothwell et al 1991) followed by inhibition of cortical motor output. Over the occipital cortex, single TMS pulses can produce phosphenes (Marg and Rudaki 1994) and can interrupt the perception of briefly presented visual stimuli.
(Amassian et al. 1989). Repetitive transcranial magnetic stimulation applied at high intensities near or over the motor area for speech in the dominant hemisphere produces speech arrest (Epstein 1998; Epstein et al. 1996; Pascual-Leone et al. 1991). Repetitive transcranial magnetic stimulation delivered over the motor cortex appears to have different effects on cortical excitability depending on the pulse frequency. Frequencies in the range of 5–20 Hz produce enhanced cortical responses, or facilitation, which is demonstrated by a decreased motor-evoked potential (MEP) threshold (Berardelli et al. 1998; Pascual-Leone et al. 1994). Repeated stimulation at frequencies of about 1 Hz produces inhibition of subsequent cortical responses (Chen et al. 1997).

The initial application of high frequency (20 Hz) rTMS over the left prefrontal cortex in depressed patients resulted in promising findings (George et al. 1995). Subsequent controlled studies of daily left prefrontal rTMS (10–20 Hz) have demonstrated significant clinical improvement in depressed patients (George et al. 1997; Pascual-Leone et al. 1996). Investigators are currently attempting to determine the parameter settings of intensity, frequency, laterality, location (Klein et al. 1999), and duration of stimulation optimal for the antidepressant effects of rTMS, with the intent of finding alternatives to electroconvulsive therapy (ECT) for at least a subgroup of patients (Grunhaus et al. 2000). In contrast to ECT, rTMS would have the advantage of not requiring anesthesia and of not inducing a seizure with its associated memory loss, and would allow better control of stimulus frequency and location (Post et al. 1999). Other studies have explored the potential use of rTMS to alleviate the symptoms of obsessive–compulsive disorder (Greenberg et al. 1997), schizophrenia (Feinsod et al. 1998; Geller et al. 1997; Hoffman et al. 1999), and posttraumatic stress disorder (McCann et al. 1998).

Investigators have used various brain imaging procedures such as single photon emission computed tomography, functional magnetic resonance imaging (fMRI), and positron emission tomography (PET) to examine how brain activity (as reflected by cerebral glucose metabolism and blood flow) is altered by rTMS during or shortly after stimulation. Increases and decreases in blood flow or metabolism have been found (Bohning et al. 1999; Fox et al. 1997; Kimbrell et al. 1999; Paus et al. 1997, 1998) depending on location and frequency of rTMS stimulation. For example, T.A. Kimbrell et al. (unpublished data) found that, relative to the increases observed with sham, 20 min of active 1-Hz rTMS in normal subjects produced global and regional decreases in cerebral glucose metabolism.

The study of the long-term effects of brain stimulation at different frequencies has in part derived from studies exploring the models of long-term potentiation (LTP) and long-term depression (LTD; Li et al. 1998; Malenka 1994, 1995), as well as the concepts of kindling and quenching (Post et al. 1997; Weiss et al. 1997). These models of neuroplasticity have provided evidence that long-term changes in neuronal excitability (depression and potentiation) can be achieved in vitro with low and high frequency stimulation, respectively, in both hippocampal and amygdala slices. Whether or not analogous changes in more global measures of neuronal excitability can be achieved with rTMS in vivo remains uncertain.

The possibility of achieving differential long-term changes in brain activity with rTMS is clinically important, as this may contribute to its potential therapeutic value in neuropsychiatric disorders associated with cerebral hyper- or hypofunction. For example, our group has examined the clinical effects of 2 weeks (10 daily or in two groups of five daily sessions over 2 weeks) of rTMS treatments at 1 Hz and 20 Hz administered at 80% of motor threshold (MT) and found opposite effects on mood (Kimbrell et al. 1999). Preliminary evidence also suggested differential clinical response as a function of baseline metabolism within depressed patients; a response to 20-Hz rTMS appeared to be associated with a pattern of baseline hypometabolism, whereas response to 1-Hz rTMS appeared to be associated with baseline hypermetabolism (Kimbrell et al. 1999).

In this study we examined the effects of 1- and 20-Hz rTMS at a higher intensity (100% MT) on regional cerebral blood flow (rCBF). An 15O water PET procedure to measure absolute rCBF was performed 72 hours after each phase of active treatment. Using the preclinical data, we predicted that 10 days of 1-Hz rTMS would decrease rCBF, whereas 20 Hz rTMS would increase rCBF in a sustained fashion.

**Methods and Materials**

**Patients**

Ten depressed patients meeting DSM-IV criteria for either bipolar disorder, depressed phase (one woman and one man; mean age = 46.0 ± 1.4 [SD]), or unipolar major depression (five women and three men; mean age = 44.4 ± 7.6 [SD]) were included. They were recruited from local as well as national referrals to the Biological Psychiatry Branch, National Institute of Mental Health (NIMH) inpatient unit (n = 6) or outpatient clinic (n = 4) for participation in the rTMS and serial imaging study. The study was approved by the Radiation Safety Committee of the National Institutes of Health (NIH) and by the institutional review board of the NIMH. All patients gave written consent for the rTMS and imaging procedures. Patients were randomized to receive 2 weeks (10 daily or in two groups of five daily sessions over 2 weeks) of rTMS treatments with 1-Hz or 20-Hz or sham rTMS. Those receiving sham first were then assigned directly to 20 Hz, whereas those on active stimulation
were crossed over to the other frequency. The 10 patients discussed in this article were the first patients to complete the rTMS treatments with both frequencies and also to complete PET scans at baseline and after each active treatment phase.

**Ratings**

Trained research assistants completed the 28-item Extended Hamilton Psychiatric Rating for Depression (Ham E; Hamilton 1960) at baseline, at the end of each 5-day period of rTMS treatment, and on the day of a PET procedure. The change from baseline to after the rTMS session was calculated for each frequency. The degree of improvement or worsening in mood after high and low frequency rTMS treatments were established by Pearson $r$.

**rTMS**

Repetitive transcranial magnetic stimulation was administered using a Cadwell (Kennewick, WA) High Speed Magnetic Stimulator with a water-cooled figure-eight coil. Following an MRI scan of the brain to exclude structural abnormalities, the active MT was determined by placing the coil over the left primary motor area and establishing the minimum amount of stimulator output necessary to cause visible movement of the flexed right thumb following at least five out of 10 single pulses. This technique is highly correlated with the procedure using surface electrodes to record the MEP (Pridmore et al 1998).

The left prefrontal cortex rTMS stimulation site was determined by measuring 5 cm anterior and in a parasagittal line from the hand motor area. Ten daily rTMS treatments were administered over the left prefrontal cortex at 100% of MT with the coil angled tangentially to the head. The sham condition was administered at 20 Hz with one wing of the figure-eight coil in contact with the scalp and at a 45° angle with respect to the head. With the coil held in this orientation over M1, TMS does not produce MEPs but does produce sensations due to stimulation of scalp nerves and muscles. This has been used as a sham in previous studies (George et al 1997; Wassermann et al 1998; T.A. Kimbrell et al, unpublished data). A visible twitch in the scalp muscle was observed during these stimulations. Active high frequency (20 Hz) stimulation was administered (2 sec on and 28 sec off) 40 times for a total of 1600 stimulations per 20-min session. One-hertz rTMS was given in a continuous train of 1600 pulses over 26 min, 40 sec. Each patient had a minimum of 3 days between 1- and 20-Hz rTMS phases.

**PET Imaging Procedures**

Patients followed a low monoamine diet for a minimum of 4 days and fasted 8 hours before each PET scan. Patients were imaged at baseline while medication free for at least 2 weeks and then 3 days following the completion of their last (10th) rTMS treatment at each frequency. Scans were acquired with a GE (Waukehasha, WI) Advance tomograph in the 3D mode (DeGrado et al 1994; Lewellen et al 1996). This scanner acquires 35 simultaneous slices with an interslice spacing of 4.25 mm and a reconstructed transverse and axial resolution of 6 mm. Image reconstruction included corrections for attenuation, random events, scatter, and dead time, and counts were converted to nCi/mL. Subject preparation included insertion of an indwelling radial artery catheter to permit measurement of the arterial input function and insertion of an intravenous catheter in the other arm for injection of $^{15}$O water. Scans were obtained in planes parallel to the canthomeatal line with head movement minimized by a thermoplastic face mask molded to each subject’s head and attached to the scanner bed. A 10-min transmission scan was obtained using two rotating Ge-68 sources to correct subsequent emission scans for attenuation. Scans were performed while subjects lay on the bed with eyes closed and ears unplugged in a quiet, darkened environment. They were instructed to monitor their mood state over the subsequent several minutes in an attempt to provide more consistency and specificity of cognitive processing during this resting state. Patients rated their level of sadness, anxiety, and alertness on an ordinal scale from 0 (“none”) to 6 (“very severe”), before and immediately following each of their five 2-min scans.

The patient’s pre- and postscan ratings did not significantly change over the course of the scanning session, suggesting that the task did not induce a transient change in mood state. None of the ordinal measures changed significantly over this interval. Each subject underwent five scans separated by 10–12 min, obtained after bolus intravenous injection of 10 mCi of $^{15}$O water. Image acquisition began when the radiotracer arrived in the head and continued for 60 sec. The arterial time–activity curve was measured with an automated blood sampling and counting system, and was used with an autoradiographic method to produce quantitative images of rCBF (Herscovitch et al 1983; Raichle et al 1983).

**Imaging Analysis**

Image analysis involved stereotactic normalization of scans followed by rCBF analyses. It was performed on a Sun SPARCstation 2 workstation (Sun Microsystems, Mountain View, CA) using Matlab (Mathworks, Sherborn, MA) with Statistical Parametric Mapping software (SPM, courtesy of MRC Cyclotron Unit, Hammersmith Hospital, London, United Kingdom) (Friston et al 1991a) for stereonormalization and SPM95 for the group analyses. ANALYZE (Mayo Foundation, Rochester, MN) and NIH- and NIMH-developed software were also used in the analysis and presentation. Global CBF (gCBF) comparisons were performed on a Macintosh (Apple Computer, Cupertino, CA) using StatView (Abacus Concepts, Berkeley, CA) and Microsoft Excel.

Scans were visually inspected for artifacts. Stereotactic normalization consisted of interpolation to 43 slices, manual roll and yaw correction, and application of a stereotactic normalization algorithm (Friston et al 1991b) that reorients images along the intercommissural plane (Friston et al 1989) and then nonlinearly warps them into the standard space corresponding to the human brain atlas of Talairach (Talairach and Tournoux 1988). These images were then smoothed with a Gaussian low-pass filter of 10 mm in-plane and 6 mm axial full width at half maximum. The resulting five sets of images for each scan session in each patient were then averaged together to produce a single mean rCBF.
image representing an integration of blood flow over 10 min of passive introspection. The rationale for working with these mean images, as opposed to a set of five repeated measures for each scan session, was the lack of a peer-reviewed method for treating a random-effects analysis of variance design in SPM. These mean images were used for all rCBF comparisons in this study. Gray matter determination for the purposes of inclusion in SPM analysis was carried out as follows: the background noise threshold (above which a voxel is presumed to be within the brain) was set at one eighth of the mean of the entire image space, and whole-brain mean was calculated using only these suprathreshold voxels. Voxels exceeding 80% of the whole-brain mean were assumed to be in gray matter. Global CBF was calculated from an average of the within-brain pixel values from 16 contiguous supratentorial slices of each patient’s scan. The border of the brain for each PET slice was determined using a semiautomated edge-finding program. The calculated gCBF (mL/min/100 g tissue) represents the whole-brain mean CBF and includes gray matter, white matter, and cerebrospinal fluid in each slice.

To determine changes in rCBF during an rTMS treatment period, a paired t test was performed in the group of 10 patients comparing mean rCBF images immediately before and 72 hours following the treatment phase in question. These paired t tests resulted in Z maps corresponding to the raw probabilities in each voxel of the null hypothesis of no change in rCBF. To correct for multiple comparisons, the Z maps were then submitted to a cluster analysis technique based on Gaussian random field theory (Friston et al 1994) with a background noise threshold (above which a voxel is presumed to be within the brain) was set at one eighth of the mean of the entire image space, and whole-brain mean was calculated using only these suprathreshold voxels. Voxels exceeding 80% of the whole-brain mean were assumed to be in gray matter. Global CBF was calculated from an average of the within-brain pixel values from 16 contiguous supratentorial slices of each patient’s scan. The border of the brain for each PET slice was determined using a semiautomated edge-finding program. The calculated gCBF (mL/min/100 g tissue) represents the whole-brain mean CBF and includes gray matter, white matter, and cerebrospinal fluid in each slice.

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Results

Global Changes in CBF following rTMS: Effects of Frequency and Order

The differences from baseline in mean gCBF 72 hours after the series of 10 treatments with 1- and 20-Hz rTMS were consistent with predictions. Twenty-hertz rTMS increased global blood flow significantly (paired t test, p < .02), whereas 1-Hz rTMS did not significantly alter global blood flow (paired t test, p < .37) relative to the respective pre-rTMS treatment baseline (Figure 1). The increases in gCBF following 20 Hz were observed regardless of whether this was the first or second treatment phase. However, there was a suggestion that prior 20-Hz stimulation may have reduced the effect of 1 Hz in decreasing rCBF: five of six patients who received 1 Hz first showed decreases, whereas two of four patients who received 1 Hz after the 20-Hz trial showed decreases.

Regional Changes in CBF

Relative to pre-rTMS treatment baseline, a PET scan 72 hours after the completion of 10 sessions of 20-Hz rTMS over the left prefrontal cortex at 100% MT showed widespread increases in rCBF. The following regions demonstrated significant rCBF elevations: the prefrontal cortex (L > R), cingulate gyrus (L >> R), and the left amygdala, as well as bilateral insula, basal ganglia, uncus, hippocampus, parahippocampus, thalamus, and cerebelum (Figure 2). Increases in rCBF were apparent over almost the entire left cingulate area (Figure 2, lower left corner), with only modest, scattered increases in the right cingulate (Figure 2, lower right corner).

The same analysis was performed to evaluate the effects of 10 daily sessions of 1-Hz rTMS on rCBF. The predicted opposite effects for 1 Hz were observed, but they were less dramatic in anatomic extent or statistical significance than the increases observed with 20-Hz rTMS. There were decreases in the following regions: small areas of the right prefrontal cortex, left medial temporal cortex, left basal ganglia, and left amygdala (Figure 3). In contrast to 20 Hz, there were no areas of significant increases following 1-Hz rTMS.

Relationship of Clinical Response to Change in rCBF

The effects of 1- and 20-Hz rTMS on clinical antidepressant response in all patients were evaluated. Change in Hamilton ratings in the same individuals following 10 rTMS treatments with 1 and 20 Hz were inversely correlated (r = -.75, p < .005). Thus, each patient who improved with 1-Hz rTMS tended to worsen with 20-Hz rTMS, or vice versa. The mean change in Hamilton score was not significant in either the 1-Hz (pre–Ham E, 28.8 ± 5.5, post–Ham E, 28.7 ± 9.0) or 20-Hz (pre–Ham E, 29.1 ± 9.1; post–Ham E, 26.8 ± 5.0) rTMS phases. Moreover, the degree of clinical response was not significantly correlated with change in blood flow in either the 1-Hz phase (r = -.12, ns) or the 20-Hz phase (r = .32, ns). In addition, when the changes in rCBF were covaried for the degree of clinical improvement, the pattern of findings in Figures 2 and 3 remained essentially unaltered (data not illustrated).

Discussion

Our findings demonstrate that 10 daily treatments of 20-Hz rTMS at 100% MT over the left prefrontal cortex in...
depressed patients significantly increase rCBF in the prefrontal cortex (L > R), the entire left cingulate gyrus, and the left amygdala, as well as bilateral uncus, hippocampus, parahippocampus, thalamus, and cerebellum, in a fashion that persists for at least 72 hours following the last treatment. As predicted, the effects on rCBF following 10 daily treatments of 1-Hz rTMS were in the opposite direction, but more circumscribed, with decreases in flow in small areas of the right prefrontal cortex, left medial temporal cortex, left basal ganglia, and left amygdala. These opposite changes in rCBF were not correlated with the degree of mood improvement in either phase.

One- and 20-Hz rTMS did have opposite effects on mood in individual patients. Patients who improved with 2 weeks of rTMS on one frequency worsened on the other \((r = -0.78, p < 0.005, n = 10)\). These results at 100% MT replicate those of Kimbrell et al (1999) at 80% MT, where 2 weeks of 1- versus 20-Hz rTMS also yielded opposite effects on mood in individual depressed patients \((r = -0.80, p < 0.004, n = 10)\). The lack of cognitive impairment in that study at 80% MT (Little et al 2000) was also mirrored in the current study at 100% MT (A.M. Speer et al, unpublished data).

Thus, high frequency stimulation over the left prefrontal cortex leads to persistent increases in rCBF over widespread areas of the brain at a considerable distance from the stimulation site. Since rTMS is thought to penetrate about 1–2 cm into the brain, as revealed by the production of MEPs at this depth (Epstein et al 1990; Marg and Rudiak 1994), these remote changes in rCBF are likely mediated transsynaptically. Consistent with this view is the relative laterality of regional changes in blood flow, with a predominance of alterations in the left versus the right prefrontal cortex and cingulate, and bidirectional changes in the left amygdala (ipsilateral) but not the right. However, 20 Hz did increase rCBF in the frontal cortex bilaterally, and surprisingly, 1-Hz rTMS decreased rCBF only in the contralateral prefrontal cortex. It is possible that the use of different rTMS parameters would lead to a different pattern of changes. Although the observed changes persisted for at least 3 days following the series of 10 rTMS treatments, the duration of the effect and whether it could be magnified or extended are not known. How these rTMS effects on rCBF relate to the current overview of the literature suggesting a laterality–frequency interaction (i.e., high frequency rTMS over the left prefrontal cortex)
corresponding increases in rCBF were present in the right prefrontal cortex, consistent with the observation that decreases in rCBF were present in the left prefrontal cortex (Asplund et al. 1997; Barker et al. 1997; Demian et al. 1999; Post et al. 2000).

The long-lasting changes that we found in rCBF may be partially analogous to the long-lasting changes in synaptic excitability demonstrated in studies using in vitro slice preparations. In hippocampal, cortical, and cerebellar slice preparations, brief high frequency stimulation leads to long-term potentiation (LTP) in neural excitability in appropriate synaptic pathways. In contrast, low frequency stimulation (1 Hz) administered for 15 min leads to long-term depression (LTD). One-hertz stimulation is able to reverse the effects of high frequency stimulation and vice versa (Christie et al. 1994; Linden 1994; Malenka 1994, 1995; O’Dell and Kandel 1994). The bidirectional reversibility of LTP and LTD is less clear in the amygdala slice preparation, where the baseline state of neural excitability can affect the direction of long-term adaptation in neural excitability as reflected in rCBF (as compared to the more robust increases following 20-Hz rTMS) could be related to the order of high and low frequency rTMS phases; the state of baseline hyperperfusion in depressed patients (i.e., a relative floor effect); or the particular rTMS parameters utilized, including variability in placement of the coil over the prefrontal cortex. This study has provided clear-cut evidence of the differential effects of frequency of rTMS on the direction of long-term adaptation in neural excitability as reflected in rCBF in depressed patients. It raises the possibility of eventual therapeutic applications of selectively activating or inhibiting specific areas of the brain in different neuropsychiatric syndromes by this noninvasive procedure. In keeping with the findings of this study, low or high frequency rTMS may be differentially utilized in attempting to reregulate dysfunctional circuits associated with baseline hyperactivity or hypoactivity, respectively.

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References


