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Antidepressant Efficacy of High and Low Frequency rTMS at 110% of Motor Threshold versus Sham Stimulation over Left Prefrontal Cortex

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ABSTRACT

Background: While the efficacy of repetitive transcranial magnetic stimulation (rTMS) at 10 Hz over the left prefrontal cortex has been repeatedly demonstrated, it is not clear that the optimal parameters for the treatment of depression have been adequately elucidated.
Objectives: We sought to assess the antidepressant effectiveness of high and low frequency at a higher intensity rTMS compared to sham in patients with moderately treatment resistant depression.
Method: The authors conducted a three-week, double-blind, randomized, sham-controlled study of 24 acutely depressed patients given either active 20 Hz ($n = 8$) or 1 Hz ($n = 8$) rTMS (at 110% of motor threshold [MT]) or sham treatments ($n = 8$) over the left prefrontal cortex. Hamilton Depression ratings were analyzed by ANOVA.
Results: Patients on both frequencies showed greater improvement than on sham, which was associated with minor increases in depression. During open continuation to allow 7 weeks of active treatment in all individuals, additional improvement was observed.
Conclusions: The results seen here using 110% of MT for 3 weeks were more robust than those of previous studies of 1-Hz or 20-Hz rTMS for 2 weeks (at 80% and 100% of MT). The results also raise the possibility that both high and low frequency rTMS over left prefrontal cortex (and not just low frequency over the right prefrontal cortex) exert antidepressant effects, but further work is required to assess what parameters may be most effective in general and for a given individual.

Introduction

The potential antidepressant effects of repetitive transcranial magnetic stimulation (rTMS) of the brain have been extensively explored, with a particular focus on therapeutic effects when administered over the left prefrontal cortex. Most studies have utilized 10-Hz at 120% motor threshold (MT) including a multi-centered industry-sponsored study that resulted in FDA approval [1] and a more recent replication study [2]. Although a number of meta-analyses [3–7] have reported overall positive effects of high frequency rTMS over left prefrontal cortex (pfc) compared with sham rTMS administration, it is possible that the optimal parameters have not yet been adequately ascertained given the relatively low remission rates achieved. Moreover, a recent meta-analysis of 1 Hz rTMS over the opposite, i.e. right, pfc concluded that such stimulation was greater than placebo and equal to that of high frequency [8].

Padberg et al. [9] indicated that higher intensities, greater number of trains, and longer durations of rTMS were all related to more effective outcomes compared with sham rTMS. The frequency of rTMS has also been explored in two previous studies by this group of 1-Hz versus 20-Hz rTMS over the left prefrontal cortex (pfc), demonstrating that individual patients responded preferentially to one frequency, but not the other as there were strong inverse relationships between degree of improvement in each individual on high versus low frequency stimulation [10,11]. These two studies were performed for only 2 weeks and at lower intensities, i.e. 80% of MT and 100% of MT, respectively.

Because these studies at lower intensities failed to reveal consistent antidepressant effects of either frequency compared with sham, we conducted a third study with two additional modifications. Stimulation was administered at 110% of MT and the

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Table 1
Patient demographics and scores on the 28-item Hamilton Depression Rating Scale at baseline at weekly intervals during blind and open treatment.

Identification number	Hospital status	Age (yrs)	Gender	Diagnosis	rTMS randomization (sham, 20 Hz, 1 Hz)	HAM-D score											
						Blind randomized phase					Open continuation phase						
						Baseline	Week 1	Week 2	Week 3	Δ Baseline	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
6	IP	40	F	UP	Sham	19	21	26	27	8	24	30	29	24	21	23	20
11	IP	32	M	UP	Sham	21	27	19	20	−1	23	28	20				
12	IP	56	M	UP	Sham	25	30	31	33	8	29	26	23	30	32	34	25
13	OP	49	F	UP	Sham	24	24	25	28	4	21	19	14	15	15	15	13
14[a]	IP	51	M	BPI	Sham	29	37	–	–	8	29	19	22	11	13	5	8
17	IP	32	F	UP	Sham	25	28	22	24	−1	23	20	23	23	28	22	23
23	IP	51	M	UP	Sham	31	32	32	37	6	30	34	28	28	28	35	
24	IP	48	M	BPII	Sham	18	18	23	28	10	22	20	17				
All sham	7 IP/1 OP	44.9 ± 9.1	3 F/5 M	BPI/1 BPII/6 UP		24.0 ± 4.6	27.1 ± 6.1	25.4 ± 4.7	29.3 ± 6.0	5.3 ± 4.2	25.1 ± 3.6	24.5 ± 5.8	22.0 ± 5.1	21.8 ± 7.4	22.8 ± 7.7	22.3 ± 11.4	17.8 ± 7.1
2	IP	34	F	BPII NOS	1 Hz	31	31	33	31	0	29	21	29	16			
5	IP	40	M	UP	1 Hz	44	48	46	38	−6	45	37					
7	IP	48	F	UP	1 Hz	32	36	27	27	−5	29	21	18	15			
9	IP	34	M	UP	1 Hz	30	18	20	19	−11	20	17	16	14			
15	OP	55	M	UP	1 Hz	27	26	25	22	−5	21	23	24	18			
16	OP	30	F	UP	1 Hz	23	26	23	24	1	16	20	13	11			
19	IP	45	F	UP	1 Hz	22	15	13	16	−6	15	10	13	9			
20	OP	31	F	UP	1 Hz	20	21	20	24	4	20	25	27				
All 1 Hz	5 IP/3 OP	39.6 ± 9.0	5 F/3 M	BPI/1 BPII/7 UP		28.6 ± 7.6	27.6 ± 10.7	25.9 ± 10.0	25.1 ± 6.9	−3.5 ± 4.8	24.4 ± 9.8	21.8 ± 7.6	20.0 ± 6.6	13.813.3			
1	IP	62	M	BPI	20 Hz	53	49	43	33	−20	39	34	29	22			
3	IP	29	M	BPII	20 Hz	40	35	38	39	−1	36						
4	IP	44	F	UP	20 Hz	37	36	39	44	7							
8	IP	40	F	BPI	20 Hz	46	42	40	39	−7	35	30	30	37			
10	IP	56	F	UP	20 Hz	35	36	42	42	7							
18	IP	48	F	BPII	20 Hz	28	35	19	22	−6	22	8					
21	OP	33	M	BPI	20 Hz	25	18	15	19	−6	25	24	17	19			
22	IP	18	F	BPII	20 Hz	22	20	28	22	0	28	32	21	11			
All 20 Hz	7 IP/1 OP	41.3 ± 14.5	5 F/3 M	3BPI/3 BPII/2 UP		35.8 ± 10.6	33.9 ± 10.4	33.0 ± 10.9	32.5 ± 10.1	−3.3 ± 8.7	30.8 ± 6.8	25.6 ± 10.5	24.3 ± 6.3	22.3 ± 10.9			
Active only	12 IP/4 OP	40.4 ± 11.7	8 F/6 M	3 BPI/4 BPII/ 9 UP		32.2 ± 9.7	30.8 ± 10.7	29.4 ± 10.8	28.8 ± 9.2	−3.4 ± 6.8	27.1 ± 9.0	23.2 ± 8.7	21.5 ± 6.5	17.2 ± 8.0			

[a] Subject 14 discontinued the blind study after 1 week due to worsening of depression symptoms.

randomized part of the study lasted for three rather than 2 weeks. At this higher intensity and longer duration of study, both 1-Hz and 20-Hz rTMS over the left pfc exhibited significantly greater antidepressant effects compared with sham stimulation, which was associated with a slight worsening of depression. Open continuation of rTMS for an additional 4 weeks in all three groups showed further positive clinical effects for a total of 7 weeks of active 1-HZ or 20-Hz rTMS over the left pfc.

Methods

Twenty-four depressed patients diagnosed by SCID interview meeting DSM-IV criteria for major depressive episode were included. Nine were bipolar (37.5%) and 15 (62.5%) were unipolar. Average age was 41.9 ± 10.9 S.D. and there were 13 (54%) females and 11 (46%) males. 19 (79%) were inpatients and 5 (21%) were studied as outpatients. Patients gave oral and written informed consent for the rTMS studies for this NIMH IRB approved study, which was conducted between October, 2000 and April, 2003.

Patients were recruited on the basis of having failed at least two previous antidepressant trials, but not electroconvulsive therapy (ECT). However, the majority of patients were much more treatment resistant, having failed multiple clinical trial in the current and previous episodes. The number of prior medication failures ranged from 2 to 27, but was not available on all patients. Patients with a history of seizure disorders or other major comorbid medical problems or psychiatric diagnoses were excluded.

Prior to the rTMS trial, baseline cerebral blood flow was measured with $H_2^{15}O$ PET and then again after 3 weeks of rTMS (data to be reported in separate manuscript). Patients were medication free for at least 2 weeks for the PET scan study and remained so for the duration of the rTMS study except for one patient (# 21 in Table 1) who was maintained on his valproate prophylaxis, Each patient's baseline scan was later categorized as either cerebrally hyper- or hypo-active based on comparison with an idealized age- and sex-matched normal volunteer [12]. Patients were randomized (independent of their PET scan findings) to receive 15 daily sessions of rTMS (five times/week) over the left prefrontal cortex with either 1-Hz ($n = 8$) or 20-Hz ($n = 8$) rTMS or sham ($n = 8$).

At baseline, the motor threshold was assessed by placing the coil over the left primary motor cortex area, and using the criteria of visible movements of the right thumb occurring on at least five of ten single pulse stimulations. When this MT was established for each individual patient, a further 10% increase was administered so that stimulation would be at 110% MT. As previously described [10,11], the left prefrontal cortex was stimulated at a point 5 cm forward from the hand area of the motor cortex and along the parasagittal plane. One-Hz rTMS was given in a continuous train of 1,600 pulses over 26 min, 40 s. Twenty-Hz stimulation was administered with 2 s on and 28 s off, 40 times, for a total of 1600 stimulations/20 min session. Stimulation was delivered by the Cadwell High Speed Magnetic Stimulator.

Patients receiving sham rTMS were further randomized to 20 Hz ($n = 4$) or 1 Hz ($n = 4$) of the sham stimulation so that the frequency of the audible click they heard would match the other groups. During this sham stimulation, the rTMS figure-of-8 coil was placed with one wing in contact with the scalp and the flat portion of the coil angled at 45° from the head which was the convention at the time and later shown to reduce the induced field by 67%–73% of active rTMS [13].

The Hamilton rating scale for Depression (HAM-D 28-item expanded version) was used by highly trained research assistants who demonstrated good interrater reliability. The HAM-D was administered at baseline and at the end of each of week of treatment. These raters and all other associated clinical ward staff were blind to both active versus sham treatment as well as to high versus low frequency of stimulation, although the M.D. (A.S.) administering the rTMS was not blind. Response was defined as 50% improvement on the HAM-D. Remission was considered a HAM-D less than 12, which is comparable to that of a 7 on the 17 item scale [14].

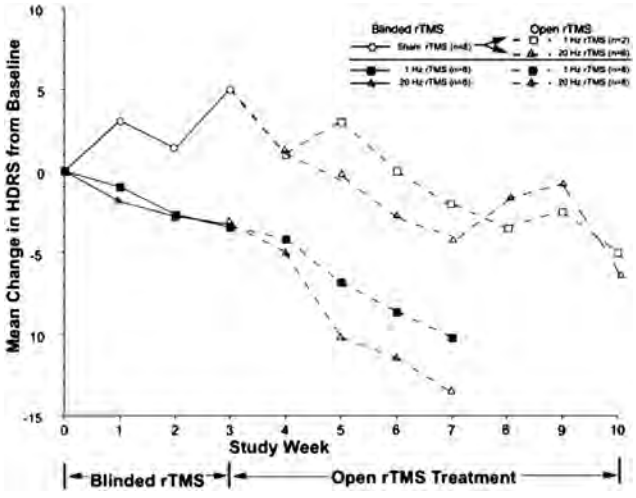

Figure 1. Improvement in depression on 1- and 20-Hz rTMS administered over left prefrontal cortex at 110% of motor threshold. HDRS Score Mean Change from Baseline: Patients randomized to active rTMS ($N = 16$) or Sham ($N = 8$). Following a 3 week single-blind phase of rTMS (1 Hz versus 20 Hz) at 110% MT, they were offered 4 weeks of open continuation at the same frequency. If they initially had sham, the active frequency, 1-Hz versus 20-Hz, was chosen based on hyperactivity or hypoactivity, respectively, seen on the baseline PET scan.

After the 3 weeks of stimulation, subjects were offered an additional 4 weeks of open treatment at the same frequency to which they had been randomized for active treatment. Those initially randomized to sham treatment were offered open continuation treatment with either high or low frequency rTMS based on their baseline PET scan results using the following rationale. Previous studies had suggested that patients with frontal lobe hypoactivity on PET scan would respond better to 20 Hz. We had earlier observed that 20-Hz rTMS increases and 1 Hz decreases cerebral blood flow, with an effect lasting at least 48 h after the last of ten rTMS treatments, thus potentially driving prefrontal activity toward the normal range if patients were matched to the appropriate frequency based on their PET results [15].

The change in HAM-D ratings from baseline to after 3 weeks of each of the randomized treatments was assessed by repeated measure ANOVA. A two-tailed value of $P < 0.05$ was considered statistically significant; using Bonferroni post-hoc analysis each frequency was compared with sham. Since there were baseline differences in severity of depression among the three groups, a mixed model for repeated measures was also run for weeks 1, 2, and 3 and at baseline.

Results

3 week blind randomized phase

As illustrated in Fig. 1 and Table 1, those randomized to sham stimulation showed a mild exacerbation of their depression over the 3 weeks of the rTMS study compared with baseline, whereas those randomized to either 1 Hz or 20 Hz active rTMS showed by ANOVA significant differences in clinical improvement ($F[2,19] = 5.27$, $P = 0.015$). Post-hoc Bonferroni multiple comparisons indicated significant differences from the sham group of the

1 Hz stimulation ($P = 0.045$) and of the 20 Hz group ($P = 0.024$); but no difference for 1 Hz versus 20 Hz. However, the baseline mean HAM-D ratings were significantly higher ($P < 0.03$) for those randomized to 20 Hz (35.8 ± 10.6), but not to 1 Hz (28.6 ± 7.6) compared to sham (24.0 ± 4.6). Therefore a mixed model with a first order autoregressive covariance structure using baseline and weeks 1, 2, and 3 HAM-D scores was run. The treatment effect was significant at a trend level ($F[2,19] = 3.172$; $P = 0.064$).

Open continuation

This trend for improvement continued or accelerated during open continuation (weeks 4–7), leading to a mean change from baseline of 13.5 points on the HAM-D for 20-Hz and 14.8 points for 1 Hz. Following the 3 weeks of sham stimulation, the six patients who were given 20-Hz stimulation and the two patients given 1-Hz stimulation for the next 7 weeks showed parallel trajectories of improvement similar to that seen in those randomized to these two frequencies initially. However, given the higher baseline HAM-D ratings after 3 weeks of sham treatment, the absolute levels of improvement achieved were not as great as those originally treated with active rTMS.

The patients randomized to active treatment initially then continued on the same frequency for an additional 4 weeks. After these 7 weeks of active treatment with 1-Hz rTMS, 50% responded and 20% remitted. In the 20-Hz group 40% responded and 30% remitted. These open observations, taken with previous findings of lesser effects at lower intensities from our lab [10,11] and Rossini et al. [16], together with Padberg's analysis [9], continue to support the view that intensity and duration of rTMS treatment, in addition to frequency are important parameters for future efficacy studies.

Discussion

3 week blind randomized phase

These data suggest that active treatment with either 1-Hz or 20-Hz rTMS for 3 weeks over the left prefrontal cortex at 110% of MT was more efficacious than sham stimulation. These findings contrast with lesser and nonsignificant antidepressant effects achieved at these same frequencies when administered at either 80% of MT or 100% of MT for only 2 weeks [10,11]. However when the findings were examined in the mixed effect repeated measures model because the 20-Hz group had more severe depression at baseline, the findings only achieved trend level significance ($P = 0.064$).

Why patients originally assigned to sham showed some worsening of their depression rather than an expected placebo effect is not apparent. However, patients were required to be off their medication for 2 week for the prior PET study and this off medication period could have contributed to the deterioration, as well as the fact that they were not immediately started in the rTMS phase for some weeks after they consented to participate. They apparently remained blind to the sham stimulation even though the angled sham is less than ideal in inducing the same degree of muscle twitching. Since the sham procedure does exert a low level magnetic field [13], it is also theoretically possible that this could have adversely affected the patients' depression, but this has not been previously observed in other studies.

The exclusion of patients with a greater level of treatment resistance from this study, i.e. these who had previously failed ECT, could also have been involved in the more significant effects in this study compared to our earlier ones [10,11] as patients with prior failure to respond to ECT were included in the earlier 1 versus 20 Hz frequencies at lower intensities of stimulation. Another possible reason for the more positive outcome in this, compared with our previous studies [10,11], could be that patients in this study were not crossed over to the opposite frequency as they were in the two previous studies. This explanation is unlikely, since if one analyzed only those patients in the previous studies who were in the first phase of randomized study (prior to any crossover), the magnitude of the antidepressant effects of active rTMS [10,11] would not have equaled those seen at 2 week in the present study.

This study is limited by its small sample size and the heterogeneous group of bipolar and unipolar depressed patients with treatment refractoriness to at least two antidepressant drug trials, but not to ECT. It was also limited by its single-blind design as the rTMS operator (A.S.), but not the raters, was aware of the active versus sham status of the patients. The method of administering the sham rTMS may also have not be ideal, as some induced current still reaches the brain [13]. These later two factors could have contributed to the unusual findings of a lack of placebo effect with some worsening of depression scores from baseline in the sham condition.

Patients did not appear to be unblinded to condition by their subjective experience of the rTMS stimulations themselves, but may ultimately been unblinded to some extent by their worsening of mood. However, once the sham group was switched to open active rTMS, their rate of improvement appeared to parallel that of the two active groups, and there was a roughly equivalent magnitude of improvement of 10.3 HAM-D points after 7 weeks of open 1 Hz rTMS and 11.5 points on 20 Hz. However, given the initial exacerbation of depression of 5.3 points, these patients in the sham first group never reached the same absolute reduction in depression ratings after 7 weeks of active rTMS treatment as did those originally randomized to either active arm.

Open continuation

Following the 3 weeks of active treatment, the trend for improvement continued or slightly accelerated during the 4 weeks of open continuation, such that after 7 weeks of active 1 Hz 50% responded and 20% remitted. In the 20 Hz group, 40% responded and 30% remitted. However, as discussed above, the 7 weeks of active treatment in those originally randomized to sham resulted in lesser degrees of absolute improvement and there was only one remitter in this group. This lower rate of remission occurred despite the fact that these sham-first patients were assigned to the frequency that theoretically would have been ideal for them based on the degree of activity on their baseline PET scan (i.e. 20 Hz for those with hypoactivity and 1 Hz for those with hyperactivity).

This analysis could not address the issue of individual predictors of clinical response to high versus low frequency rTMS as a function of either clinical characteristics or baseline PET scans [10,11] because of the small sample size.

Overview

Although both 1-Hz and 20-Hz stimulation over the left pfc in this study induced a similar magnitude of antidepressant effects at 3 weeks and after a total of 7 weeks of rTMS, it remains an open issue as to whether either of these frequencies would match the effectiveness of the intermediate frequency of 10 Hz at 120% of MT (which has been both FDA approved and widely used in studies evaluating the comparative effects of rTMS and ECT) [17–22]. While McLoughlin et al. [21] and Grunhaus et al. [18], found lesser degrees of response to rTMS than ECT, they included patients with psychotic depression. Keshtkar et al. [23] reported superior effects of ECT, but rTMS was administered at 80% of MT and at an unspecified frequency. All of these comparative studies reported negligible effects of rTMS on cognition in contrast to some impairment with ECT.

Whether some patients would have responded more dramatically or preferentially to 1-Hz or 20-Hz rTMS as previously observed [10,11] compared to the frequency to which they were initially randomized requires further study in larger number of individuals and utilizing cross-overs. When McDonald et al. [24] crossed non-remitters to high frequency (10 Hz) rTMS (over left prefrontal cortex) over to low (1 Hz) rTMS over the right prefrontal cortex, they achieved at 30.5% remission rate. This magnitude of response is similar to that achieved in rTMS-native patients in their first phase of treatment. The McDonald et al. [24] study adds further support to the idea that different patients might respond preferentially to either high/intermediate versus low frequency rTMS.

However, to the extent that 20 Hz and 1 Hz both exerted similar magnitude antidepressant effects when administered over the left prefrontal cortex in our study, raises the question of why this might be so when previous studies have indicated lesser response of 1 Hz over left pfc, [25,26] and a good response of 1 Hz over the right pfc [24]. The recent meta-analysis of Berlim et al. concluded that 1 Hz rTMS over the right pfc was superior to sham and equal to 10 Hz over the left pfc [8]. Our data suggest the possibility that 1 Hz over the left pfc is also effective and suggest that the proposition that low frequency rTMS is only effective when given over the right pfc should be further evaluated.

Moreover, the preliminary findings of our study raise some interesting and puzzling conceptual issues. Twenty-Hz rTMS increases brain activity measured by rCBF on PET bilaterally in a widespread fashion, while 1-Hz decreases activity bilaterally. This effect lasted at least 48 h after the last rTMS in our previous study at 100% MT [15]. Thus, the question remains, why should both high and low frequency rTMS, which exert opposite effects on brain activity, induce roughly similar degrees of antidepressant response? Does merely driving brain activity either higher or lower than baseline convey a therapeutic effect directly or by inducing an adaptive response, or, contrarily, is some normalization of activity required? The current findings of apparent response to both high and low frequency rTMS over left pfc also raises the question as to whether rTMS over the right pfc [8,27] specifically requires low frequencies in order to induce antidepressant effects, and whether both high and low frequency rTMS might be effective over either cortex.

The idea of low frequency rTMS effectiveness selectively over the right prefrontal cortex is predicated on the existence of cerebral laterality differences is depression; yet some patients may not show this hemispheric laterality difference. Another possible reason that 1 Hz rTMS could be effective over either cortex could relate to the long term changes in synaptic excitability presumedly induced in vivo, similar to those seen in in vitro slice preparations. In the hippocampus, 20 Hz induces long term potentiation (LTP) and 1 Hz induces long term depression (LTD). However, in the amygdala 1 Hz induces not LTD, but LTP. Remarkably, if the amygdala slice is first stimulated with a high frequency burst, then 1 Hz induces the opposite effect of LTD [28]. This phenomenon is called metaplasticity, and it is possible that different states of amygdala excitability based on differences in prior experience could similarly be modulated in opposite directions by the same 1 Hz stimulation.

Whether 20-Hz or 1-Hz rTMS is more or less effective in depression than the currently accepted frequency of 10-Hz remains to be further studied, as does the utility of matching patients to their own baseline level of brain activity [9,10], or even more precisely to their own alpha frequency [29]. This line of clinical research might require new methodological approaches to sequential parameter explorations in individual patients to formulate hypotheses that can then be tested in more classical large-scale, sham-controlled research clinical trials [30–32]. In this regard, comparative and crossover studies may be more productive than traditional designs, especially when seeking new approaches to the most treatment-refractory patients [33].

Nonetheless, this study provides further support for higher (110% of MT) compared with lower intensity (80–100% of MT) rTMS [9,10] inducing antidepressant effects, and improvement continuing during longer periods of stimulation beyond 2 and 3 weeks. The optimal rTMS frequencies over the left and right prefrontal cortex administered either alone or sequentially, and how one might proceed with more extended rTMS treatment for continuation and prophylaxis in those initially responsive to acute treatment, also remain continuing important questions [34,35].

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