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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.
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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.

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