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**Transcranial Magnetic Stimulation (TMS)  
in the Treatment of Pharmacoresistant  
Major Depression:  
Examination of Cognitive Function During  
Acute Treatment**

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# Transcranial Magnetic Stimulation (TMS) in the Treatment of Pharmacoresistant Major Depression: Examination of Cognitive Function During Acute Treatment

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## Abstract

**Objective:** TMS is safe and effective in patients with major depression (MDD) who have failed to receive benefit from initial pharmacotherapy. In this report, we provide additional evidence of the effect of TMS on cognitive function during acute treatment.

**Methods:** Cognitive function was examined in a multisite, randomized controlled trial of NeuroStar TMS therapy in patients with pharmacoresistant MDD (O'Reardon, 2007) (N=155 active TMS, N=146 sham TMS). Specific measures of global cognition (Mini Mental Status Examination), short-term (Buschke Selective Reminding Test) and long-term (Autobiographical Memory Interview-Short Form) memory were obtained prior to first treatment, and at 4 and 6 weeks during an acute treatment course of daily, left prefrontal TMS.

**Results:** There was no deterioration within or between treatment groups on any measure of cognition during acute treatment. Additionally, each treatment group was stratified by clinical outcome (HAMD24 responder) at the end of 6 weeks. Within the TMS group only, there was a statistically significant improvement on the BSRT in the TMS responders compared to TMS non-responders for both short-term recall ( $P = 0.0116$  at 4 weeks;  $P = 0.0038$  at 6 weeks) and delayed recall ( $P = 0.0463$  at 4 weeks;  $P = 0.0012$  at 6 weeks). This improvement in cognitive function was not seen in sham treated patients ( $P = \text{NS}$  at both 4 and 6 weeks).

**Conclusions:** These results suggest that clinical recovery with active TMS is associated with an improvement in short-term verbal memory that cannot be fully accounted for by improvement in mood.

Clinical trial posted on [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Listing No. NCT 00104611. Supported by a grant from Neuronetics, Inc.

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## Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive method used to electrically stimulate superficial cortical neurons, using rapidly alternating magnetic fields generated in a strong magnetic coil held in contact with the scalp (Figure 1). A large number of randomized controlled trials (RCTs), which have been aggregated in several published meta-analyses, support the antidepressant effect of TMS in patients with major depression when it is used in daily sessions over several weeks directed to the dorsolateral prefrontal cortex (DLPFC). Our group has recently reported the overall results of a large, multisite RCT of TMS in the treatment of pharmacoresistant major depression. The results of that work demonstrated that TMS is a safe and effective treatment, and led to the recent FDA clearance of the NeuroStar TMS Therapy system.

Because TMS involves the delivery of electric current through the cortex, it is reasonable to ask whether this antidepressant treatment may have adverse effects on cognitive function. Electroconvulsive therapy (ECT) also results in the delivery of electric current to the brain, however, the distribution of current flow during a routine session of ECT traverses much broader areas of brain substance than occurs during a TMS treatment session, and is also associated with the induction of a convulsion. In addition, ECT, unlike TMS, is administered under anesthesia. Not surprisingly, it is well-known that ECT is routinely accompanied by profound changes in global cognitive function universally in the acute aftermath of a session, and that in some patients, deficits in long-term memory may persist long after the cessation of the last treatment session, and are therefore permanently lost for the individual.

In contrast, the procedure of TMS does not involve the use of pre-medication, or any during-treatment sedation or anesthesia. In addition, because the electrical current is delivered via the

use of pulsed magnetic fields, the induced electric current is delivered in a more anatomically discrete manner to a limited region of the superficial cerebral cortex located just beneath the treatment coil, and TMS is not associated with a convulsion under normal conditions of use.

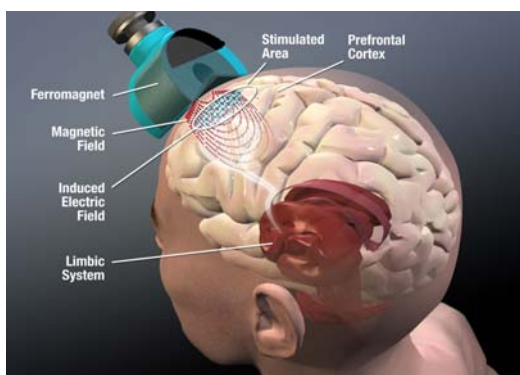
Prior research has described the cognitive outcomes observed after TMS administration. For example, Martis and colleagues reported on a baseline and post-treatment neurocognitive battery administered to 15 medication-free patients treated with left prefrontal stimulation for 2 to 4 weeks (10 pps, 20 trains: 5 seconds on/30 seconds off, 110% MT). They noted no evidence of cognitive worsening with TMS, on the contrary they reported statistically significant improvement in measures of working memory-executive function, objective memory and fine motor speed domains.

Hausmann described the cognitive outcomes following an aggressive TMS study performed as an add-on to ongoing ineffective pharmacotherapy. Forty-one patients were studied with either of two active TMS treatment regimens (either left prefrontal 20 pps, 10 trains: 10 seconds on/90 seconds off, 100% MT, or a combined high and low frequency protocol to both left and right prefrontal, 1pps, 1 train: 10 minutes on), both administered for 10 sessions. A more favorable outcome for encoding verbal memory was noted in the active treated patients.

Finally, Schulze-Rauschenbach has reported the outcome in 30 patients given either 10 sessions with high frequency left prefrontal TMS (10 pps, 20-30 trains: 2 seconds on/5 seconds off, 100% MT) or 10 sessions of unilateral ECT. The patients treated with TMS showed either stable or improved cognitive performance, and an alleviation of baseline complaints of memory function, while memory recall and cognitive complaints deteriorated in the ECT treated group.

In the present report, we expand on these observations by reporting the cognitive function outcomes in the aftermath of an acute treatment course of TMS using the NeuroStar TMS Therapy system in patients with pharmacoresistant major depression. Global cognitive function was assessed using the Mini Mental Status Exam, short-term memory was evaluated using the Buschke Selective Reminding Test, and long-term memory was examined with the Autobiographical Memory Interview-Short Form. These specific cognitive tests were selected for study based on prior evidence of their sensitivity to change during studies of the cognitive outcome of ECT.

**Figure 1. Transcranial Magnetic Stimulation**



- Pulsed magnetic fields of ~1.5 Tesla in strength
- Magnetic fields pass unimpeded approximately 2-3 cm into cortex
- Induces a focal electrical current in cortical tissue
- Produces local and distal functional changes on the target neural circuitry

## Methods

### Randomized Clinical Trial Design

The overall clinical development program for the NeuroStar TMS Therapy system has been previously reported (O'Reardon, et al, 2007). The study included a randomized, sham-controlled trial examining the efficacy and safety of 6 weeks of acute treatment (5x/week, 30 sessions total exposure) with NeuroStar TMS. The overall safety exposure population was comprised of 323 patients, while N=301 patients formed the evaluable patient dataset, defined as those patients with a baseline and at least one post-baseline efficacy assessment. The treatment parameters included stimulation at 120% of observed motor threshold, applied at a pulse frequency of 10 pulses per second (4 seconds on time and 26 seconds off time), for a total of 3000 pulses per treatment session. Efficacy was determined using both the Montgomery-Asberg Depression Rating Scale and the 17 and 24-item versions of the Hamilton Depression Rating Scale. Major inclusion and exclusion criteria for the study population are shown in Table 1. Overall demographic and clinical features of the study safety

population at baseline are shown in Table 2. Cognitive function was determined using the Mini Mental Status Exam (MMSE) to assess global cognitive function, the Buschke Selective Reminding Test (BSRT) to assess short-term recall, and the Autobiographical Memory Interview – Short Form (AMI-SF) to assess long term memory. These tests were performed at baseline, and after 4 weeks and 6 weeks of acute treatment. Multiple versions of the MMSE and BSRT were used to deter learning effects.

### Statistical Analysis

Safety analyses were performed on the strict intent-to-treat sample of all patients contained in the evaluable study population. Changes in specific cognitive function scores were tested with an analysis of covariance, using baseline score as a fixed effect covariate, adjusting for site differences using a random effect. After examination of the overall differences in cognitive outcome for the active compared to sham treatment conditions, an exploratory analysis was performed within each group by stratifying the treatment group according to their HAMD-24 responder status at the end of acute treatment (6 week) time point. T-tests were used to examine the contrasts within and between groups in this exploratory analysis. Cognitive function measures are analyzed here as non-transformed raw data.

**Table 1. Study Population Selection Criteria**

<b>INCLUSION CRITERIA</b>
<p><u>Primary Diagnosis:</u></p> <ul style="list-style-type: none"> <li>• DSM-IV Major Depressive Episode</li> <li>• Current episode &lt; 3 years</li> </ul> <p><u>Symptom Severity:</u></p> <ul style="list-style-type: none"> <li>• HAMD17 <math>\geq</math> 20 (Item 1 <math>\geq</math> 2)</li> <li>• CGI-S <math>\geq</math> 4 (moderate or greater severity)</li> </ul> <p><u>Prior Treatment Failure:</u></p> <ul style="list-style-type: none"> <li>• History of &gt; 1 and &lt; 4 antidepressant rx's of adequate dose and duration in current episode (by ATHF criteria)</li> </ul>
<b>EXCLUSION CRITERIA</b>
<p><u>Psychiatric:</u></p> <ul style="list-style-type: none"> <li>• Psychosis</li> <li>• Bipolar Disorder</li> <li>• Obsessive compulsive disorder</li> <li>• Post-traumatic stress disorder (past year)</li> <li>• Prior ECT failure or recent ECT Rx</li> <li>• Immediate risk of suicide</li> <li>• Unable to discontinue psychotropic meds</li> <li>• Mini Mental Status Exam total score &lt; 24</li> </ul> <p><u>Non-Psychiatric:</u></p> <ul style="list-style-type: none"> <li>• Unstable medical disease</li> <li>• Neurological disease (incr in seizure risk)</li> <li>• Metal objects in head</li> </ul>

**Table 2. Demographic and Clinical Features of the Safety Exposure Population**

Variable Name	Treatment Group		P-Value
	Active TMS (N=165)	Sham TMS (N=158)	
<b>Demographic Variables N (%)</b>			
Female	91 (55.2)	80 (50.0)	0.375
Age [yrs, mean (SD)]	48.2 (10.9)	48.3 (11.1)	0.887
<b>Ethnic Origin N (%)</b>			
Caucasian	156 (94.5)	143 (89.4)	0.103
Other	9 (5.5)	17 (10.6)	
<b>Clinical Variables</b>			
Recurrent illness course (%)	158 (95.8)	150 (93.8)	0.463
Duration of current episode $\geq$ 24 months N (%)	24 (15.0)	38 (23.0)	0.068
Mean number of all antidepressant treatments in current episode	5.5 (3.4)	5.5 (4.0)	1.000
Mean number of ATHF-verified adequate exposure antidepressant treatments in current episode	1.6	1.6	1.000
<b>Cognitive Function</b>			
Mini Mental Status Exam Total Score [mean (SD)]	28.4 (1.6)	28.5 (1.4)	0.552
<b>Baseline Symptom Severity</b>			
MADRS Total Score [mean (SD)]	32.6 (5.3)	33.0 (5.7)	0.479
HAMD24 Total Score [mean (SD)]	30.7 (3.9)	30.6 (4.4)	0.836
HAMD17 Total Score [mean (SD)]	22.7 (2.4)	22.9 (3.1)	0.466
CGI-Severity Score [mean (SD)]	4.7 (0.6)	4.7 (0.7)	0.595
IDS-SR Total Score [mean (SD)]	42.1 (9.5)	43.4 (10.0)	0.152

**Results**

There was no deterioration within or between treatment groups on any measure of cognition during acute treatment in the pre-specified analysis of the overall safety exposure population (Tables 3a-d). An additional exploratory analysis was then conducted on the evaluable patient population in each treatment group, stratified by clinical outcome (HAMD24) responder vs HAMD24 non-responder) at the end of 6 weeks of acute treatment. Within the TMS group only, there was a statistically significant improvement on the BSRT in the TMS responders compared to TMS non-responders for both short-term recall (P = 0.0116 at 4 weeks; P = 0.0038 at 6 weeks) and delayed recall (P = 0.0463 at 4 weeks; P = 0.0012 at 6 weeks). This improvement in cognitive function was not seen in sham treated patients (P = NS at both 4 and 6 weeks).

**Table 3a. Cognitive Function Outcomes: Amnesia Scores (AMI-Short Form)**

	NeuroStar TMS (N=155)			Sham TMS (N=146)			
		Baseline	Week 4	Week 6	Baseline	Week 4	Week 6
<b>Overall Group</b>	<b>Mean</b>	--	88.8	88.5	--	88.9	89.8
<b>(Safety Exposure Pop'n)</b>	<b>SD</b>		9.0	8.7		8.8	8.1
	<b>P-Value (0)</b>					0.938	0.353
<b>HAMD24 Responder</b>	<b>Mean</b>	--	87.5	88.9	--	88.1	86.6
<b>(Evaluable Pop'n)</b>	<b>SD</b>		10.3	8.4		8.0	7.7
	<b>P-Value (1)</b>					0.837	0.306
<b>HAMD24 Non-Responder</b>	<b>Mean</b>	--	89.2	88.2	--	89.0	91.6
<b>(Evaluable Pop'n)</b>	<b>SD</b>		8.6	9.0		9.0	7.9
	<b>P-Value (2)</b>		0.340	0.703		0.650	0.022 (NR>R)

**Table 3b. Cognitive Function Outcomes: Total Score (MMSE)**

		NeuroStar TMS (N=155)			Sham TMS (N=146)		
		Baseline	Week 4	Week 6	Baseline	Week 4	Week 6
<b>Overall Group</b> (Safety Exposure Pop'n)	<b>Mean</b>	28.5	28.5	28.8	28.4	28.4	28.4
	<b>SD</b>	1.5	1.6	1.4	1.7	1.6	1.8
	<b>P-Value (0)</b>				0.552	0.474	0.025 (Act>Sham)
<b>HAMD24 Responder</b> (Evaluable Pop'n)	<b>Mean</b>	28.5	29.0	29.1	29.0	28.5	28.4
	<b>SD</b>	1.45	1.28	1.32	1.13	1.74	2.34
	<b>P-Value (1)</b>				0.256	0.123	0.087 (Act>Sham)
<b>HAMD24 Non-Responder</b> (Evaluable Pop'n)	<b>Mean</b>	28.6	28.3	28.7	28.4	28.3	28.4
	<b>SD</b>	1.39	1.67	1.46	1.70	1.58	1.64
	<b>P-Value (2)</b>	0.918	0.031 (R>NR)	0.097 (R>NR)	0.124	0.736	0.467

**Table 3c. Cognitive Function Outcomes: Short-Term Recall (BSRT)**

		NeuroStar TMS (N=155)			Sham TMS (N=146)		
		Baseline	Week 4	Week 6	Baseline	Week 4	Week 6
<b>Overall Group</b> (Safety Exposure Pop'n)	<b>Mean</b>	47.6	49.1	49.4	47.4	49.1	49.1
	<b>SD</b>	12.3	12.3	12.3	13.3	12.5	12.9
	<b>P-Value (0)</b>				0.920	0.987	0.929
<b>HAMD24 Responder</b> (Evaluable Pop'n)	<b>Mean</b>	45.4	50.7	51.5	48.8	50.3	50.5
	<b>SD</b>	13.08	12.98	13.59	10.02	10.46	9.27
	<b>P-Value (1)</b>				0.298	0.190	0.169
<b>HAMD24 Non-Responder</b> (Evaluable Pop'n)	<b>Mean</b>	48.7	48.0	47.9	47.1	48.9	48.4
	<b>SD</b>	12.06	12.84	13.35	13.60	12.88	14.12
	<b>P-Value (2)</b>	0.160	0.015 (R>NR)	0.006 (R>NR)	0.588	0.899	0.772

**P-Value (0)** = Change from baseline ANOVA between-group contrast NeuroStar TMS vs Sham TMS

**P-Value (1)** = Between-group contrast between NeuroStar TMS and Sham TMS treatment condition Responders

**P-Value (2)** = Within-group contrast between Responder and Non-Responder conditions

**Table 3d. Cognitive Function Outcomes: Delayed Recall (BSRT)**

	NeuroStar TMS (N=155)			Sham TMS (N=146)			
		Baseline	Week 4	Week 6	Baseline	Week 4	Week 6
<b>Overall Group</b> (Safety Exposure Pop'n)	<b>Mean</b>	7.0	6.7	6.8	7.5	7.5	7.1
	<b>SD</b>	3.1	3.4	3.4	2.9	2.9	2.8
	<b>P-Value (0)</b>				0.165	0.352	0.813
<b>HAMD24 Responder</b> (Evaluable Pop'n)	<b>Mean</b>	6.4	7.1	7.6	7.6	7.6	6.8
	<b>SD</b>	3.36	3.56	3.12	2.59	2.50	2.93
	<b>P-Value (1)</b>				0.146	0.605	0.014 (Act>Sham)
<b>HAMD24 Non-Responder</b> (Evaluable Pop'n)	<b>Mean</b>	7.2	6.5	6.4	7.4	7.4	7.1
	<b>SD</b>	3.04	3.43	3.48	2.97	2.94	2.86
	<b>P-Value (2)</b>	0.164	0.041 (R>NR)	0.001 (R>NR)	0.739	0.862	0.366

**P-Value (0)** = Change from baseline ANOVA between-group contrast NeuroStar TMS vs Sham TMS  
**P-Value (1)** = Between-group contrast between NeuroStar TMS and Sham TMS treatment condition Responders  
**P-Value (2)** = Within-group contrast between Responder and Non-Responder conditions

**Conclusions**

- There was no significant difference between active TMS and sham TMS treatment conditions during the randomized, controlled acute treatment study on any cognitive outcome measure
- Nevertheless, stratifying the treatment groups by final response outcome suggests that clinical recovery with active TMS may be associated with an improvement in global cognitive function and in short-term verbal memory that cannot be fully accounted for by improvement in mood.

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