Right Versus Left Prefrontal Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: A Preliminary Investigation

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Background: There is preliminary evidence that repetitive transcranial magnetic stimulation (rTMS) may be useful for the treatment of obsessive-compulsive disorder (OCD), but no definitive study has been published, and the effect of laterality of stimulation is uncertain.

Method: Subjects (N = 12) with resistant OCD were allocated randomly to either right or left prefrontal rTMS daily for 2 weeks and were assessed by an independent rater at 1 and 2 weeks and 1 month later.

Results: Subjects had an overall significant improvement in the obsessions ($p < .01$), compulsions ($p < .01$), and total ($p < .01$) scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) after 2 weeks and at 1-month follow-up. This improvement was significant for obsessions ($p < .05$) and tended to significance for total Y-BOCS scores ($p = .06$) after correction for changes in depression scores on the Montgomery-Asberg Depression Rating Scale. There was no significant difference between right- and left-sided rTMS on any of the parameters examined. Two subjects (33%) in each group showed a clinically significant improvement that persisted at 1 month but with relapse later in 1 subject.

Conclusion: A proportion (about one quarter) of patients with resistant OCD appear to respond to rTMS to either prefrontal lobe, although in the absence of a sham treatment group in this study, we cannot rule out the possibility of this being a placebo response. This treatment warrants further investigation to better establish its efficacy and examine the best parameters for response.

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In spite of recent advances in the treatment of obsessive-compulsive disorder (OCD), a substantial proportion of patients continue to be resistant to treatment,[1] warranting the exploration of new therapies. One such potential treatment is repetitive transcranial magnetic stimulation (rTMS), which has hitherto been studied extensively for depressive disorders.[2] The application of rTMS to OCD is also of interest in view of the functional neuroanatomy of OCD, with the consistently reported hypermetabolism in the prefrontal cortex that normalizes with treatment.[3]

One published study of rTMS in OCD reported reduction of compulsive urges for 8 hours after 1 session of rTMS on the right prefrontal cortex, but not the left prefrontal cortex or the mid-occipital region.[4] This was a modest and transient effect after a single session of stimulation, which was restricted to compulsive urges, with no effect on obsessional thoughts, and its clinical relevance was unclear. To further investigate the issue of differential effect of right versus left stimulation, and to determine the clinical implications of such a response, we conducted a 2-week study using stimulation parameters similar to those previously used in rTMS studies for depression.

Table 1. Results of 2 Weeks of rTMS to Right and Left Prefrontal Cortices in Subjects With OCD[a]

	Patients Given Right-Sided Stimulation (N = 6)[b]				Patients Given Left-Sided Stimulation (N = 6)[b]				Dependent Variable Scores Across Rating Occasions for All Patients (N = 12)[b]				
Dependent Measures	Baseline	Week 1	Week 2	1-Month Follow-Up	Baseline	Week 1	Week 2	1-Month Follow-Up	Baseline	Week 1	Week 2	1-Month Follow-Up	Significance (linear trend)
Y-BOCS													
Obsessions subscale	14.83 (2.93)	9.50 (3.73)	10.33 (3.93)	7.40 (1.82)	12.50 (1.64)	9.83 (6.01)	8.00 (6.60)	9.50 (4.46)	13.46 (2.57)	9.69 (4.57)	9.23 (5.10)	8.17 (3.61)	F = 14.288, df(1,12) p = .004
Compulsions subscale	12.33 (6.65)	9.33 (6.44)	6.67 (5.01)	4.60 (3.36)	10.00 (5.14)	8.17 (6.52)	8.67 (6.31)	7.00 (4.47)	10.69 (5.81)	8.46 (6.04)	7.46 (5.35)	5.83 (3.83)	F = 14.090, df(1,12) p = .005
Total	27.17 (8.95)	18.83 (8.98)	17.00 (4.86)	12.00 (3.94)	22.50 (6.25)	18.00 (12.18)	16.67 (12.31)	16.50 (8.31)	24.15 (7.81)	18.15 (9.82)	16.69 (8.56)	14.00 (6.67)	F = 15.485, df(1,12) p = .003
STAI-S	68.83 (14.86)	48.50 (13.05)	45.50 (9.67)	44.50 (18.96)	54.33 (13.56)	44.67 (13.88)	45.00 (15.02)	45.33 (12.72)	59.08 (14.44)	46.58 (13.00)	45.25 (12.05)	45.29 (14.35)	F = 6.724, df(1,12) p = .029
BDI	23.2 (12.50)	15.25 (6.60)	14.17 (8.91)	11.60 (14.64)	19.67 (12.55)	10.17 (5.91)	9.67 (8.26)	10.83 (7.78)	21.00 (11.50)	12.45 (6.12)	12.15 (8.20)	11.33 (10.29)	F = 5.099, df(1,12) p = .054
MADRS	16.67 (8.69)	10.83 (6.79)	15.33 (10.35)	12.20 (8.81)	10.67 (6.80)	5.67 (5.09)	6.00 (7.51)	6.83 (5.71)	12.77 (8.38)	8.46 (6.10)	10.38 (9.54)	8.83 (7.25)	F = 1.719, df(1,12) p = .222

[a]The results for all patients on a repeated-measures analysis of variance are presented in the right-hand column. Abbreviations: BDI = Beck Depression Inventory, MADRS = Montgomery-Asberg Depression Rating Scale, OCD = obsessive-compulsive disorder, rTMS = repetitive transcranial magnetic stimulation, STAI-S = Spielberger State-Trait Anxiety Inventory–State, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.
[b]All rating scale scores are mean (SD).

METHOD

Subjects

Subjects were 12 right-handed individuals who were diagnosed with OCD by 2 psychiatrists and met DSM-IV criteria for this disorder. They did not concurrently meet DSM-IV criteria for major depressive disorder. Subjects had a mean age of 40.5 years (SD = 13.4 years), and 9 (75%) were male. They had suffered from OCD for a mean period of 17.3 years (range, 1–58 years), and in 7 subjects (58%), the illness had been unremitting. Nine subjects (75%) had had a comorbid depressive episode in the past, but there was no history of psychosis, substance abuse, or tic disorders. They were medically well and had no history of rheumatic fever, head injury, or epilepsy. They had all received antiobsessional drugs in the past, with a mean of 5.2 drugs having been tried. They had also failed a mean of 0.8 trials (SD = 0.4) of cognitive-behavioral therapy. Ten subjects were taking medication (alprazolam, amitriptyline, atenolol, clomipramine, clonazepam, citalopram, fluoxetine, fluvoxamine, omeprazole, periciazine, risperidone, and sertraline) and had been maintained on a constant dose for 8 weeks prior to and during the period of the study. Their symptom ratings are presented in Table 1. All subjects gave written consent to participate in the study, and the study was approved by the Institutional Ethics Committee of the South Eastern Sydney Area Health Service, Eastern Section.

Design

Subjects were randomly allocated to 2 weeks of right or left prefrontal stimulation. Subjects were informed that they would receive real rTMS but were ignorant of the implications of laterality. rTMS was given daily on consecutive weekdays (5 sessions per week). Stimulation parameters were 10 Hz, 30 trains of 5 seconds each, 25 seconds between trains, and 110% resting motor threshold. A 70-mm figure 8–shaped stimulating coil (Magstim Co., Whitland, Dyfed, Wales, U.K.) was centered over the left or right dorsolateral prefrontal cortex, defined as 5-cm anterior to the optimal site for activating the right or left first dorsal interosseus muscle.[5] The coil was positioned tangential to the scalp with its extensions perpendicular to a line running from the stimulation site to the subject's nose.

Ratings

Subjects were rated by a psychiatrist at baseline and after 1 and 2 weeks of stimulation and 1 month after the completion of the treatment. The rater was blind to the side of stimulation. The following instruments were used: the Yale-Brown Obsessive Compulsive Scale (Y-BOCS),[6,7] the Montgomery-Asberg Depression Rating Scale (MADRS),[8] the Beck Depression Inventory (BDI),[9] and the Spielberger State-Trait Anxiety Inventory–State.[10] All subjects completed 2 weeks of stimulation; 1 subject had a subsequent 4-week course after a 3-month interval.

Analysis

We used repeated-measures analysis of variance to evaluate time-dependent effects on obsessions and compulsions indices on the Y-BOCS and contrasts for side of stimulation. Ratings on the MADRS were used as covariates to examine the effect of changes in depression on obsessive-compulsive symptoms. All analyses were performed using the Statistical Package for Social Sciences (version 10.0 for Windows).[11]

RESULTS

The results are presented in Table 1. There was no significant difference between right and left stimulation on the

overall Y-BOCS scale scores ($F = 0.005$, $df = 1,12$; $p = .947$) or any of the other ratings. Both groups demonstrated a significant reduction in obsessions ($F = 14.288$, $df = 1,12$; $p = .004$) and compulsions ($F = 14.090$, $df = 1,12$; $p = .005$) Y-BOCS scores over the 2 weeks. All 12 subjects were analyzed together and showed a significant linear trend toward improvement at up to 4 weeks of follow-up ($F = 15.485$, $df = 1,12$; $p = .003$), which tended toward significance ($p = .062$) when the MADRS scores were used as covariates. The latter reflected a significant reduction in obsessions ($F = 9.031$, $df = 1,12$; $p = .03$), but a nonsignificant reduction in compulsions ($F = 3.311$, $df = 1,12$; $p = .128$) at up to 4 weeks of follow-up with the MADRS score entered as a covariate.

When examined individually, 4 (33%) subjects had a clinically significant improvement (2 right and 2 left), defined as a reduction in Y-BOCS scores > 40%, which was maintained at 1 month of follow-up. Two of these (1 each for right and left stimulation) had an almost complete remission at 2 weeks (total Y-BOCS scores of 0 and 4 from baseline scores of 10 and 24, respectively), but 1 (left-sided stimulation) relapsed after 6 weeks and went on to have a second 4-week course of treatment, with a less marked, albeit clinically significant, improvement. A conservative conclusion is that one fourth of the patients had sustained improvement with rTMS.

The stimulation was generally well tolerated by the subjects, with 3 reporting headache immediately after the treatment that warranted analgesic treatment with good response. There were no dropouts, no seizure was observed, and no subject reported adverse effects on memory or concentration.

DISCUSSION

This study indicates that rTMS may be of benefit in OCD patients resistant to conventional treatments. Both obsessions and compulsions improved with right or left prefrontal stimulation. Indeed, a clinically significant and sustained improvement was observed in one fourth of the patients, a result similar to that reported with neurosurgical treatment.[12,13] This change is unlikely to be the consequence of a nonspecific antidepressant effect (even though some depressive symptoms diminished), as none of the subjects had clinically diagnosed major depression at baseline. The improvement in obsessions was significant even after correction for change in depression scores. The improvement in compulsions, while significant when uncorrected for depression, did not reach significance when the MADRS scores were entered as covariates.

These are results from a study with notable limitations, namely an open design and a small sample size. Naturally, this introduces the possibility that both groups experienced a placebo response. This possibility cannot be discounted even though OCD patients are recognized to have a low placebo response[14] and these patients had been ill for long periods of time and had unsuccessfully tried many treatments previously. Furthermore, clinical improvement was gradual, continuing into the second week of treatment, and then persisting for at least 1 month after its completion. One subject relapsed, but improved substantially upon receiving a second course of rTMS using identical parameters as before. Four patients experienced improvement that was sustained at 1 month, beyond levels achieved previously.

Our study used rTMS at an intensity and frequency that has been applied to studies of depression.[5] Given the preliminary nature of investigations in this field, we used parameters that have been demonstrated to produce behavioral effects in treatment studies. The lack of a laterality effect in our study is important for future studies of OCD, as the best site of stimulation remains to be determined. Our finding is contrary to the study by Greenberg et al.,[4] which reported a reduction in compulsive urges after a single session of right but not left prefrontal stimulation. Our subjects did not report any change after a single session, but the improvement was evident after 5 days of daily stimulation. The 2 studies are, therefore, not strictly comparable, and further studies are needed to settle this issue.

Studies of the functional neuroanatomy of OCD do not clearly suggest a laterality of pathologic processes, and bilateral disturbances have been described in neuroimaging studies.[3] For the neurosurgical treatment of OCD, a clear laterality effect is again not reported, with most patients who improve having received bilateral lesions.[15] The lack of difference between the effects of left- and right-sided prefrontal rapid rTMS in our study is therefore not inconsistent with the general published literature on OCD. These findings lead us to speculate that bilateral prefrontal simulation, using a double-cone coil with suprathreshold stimulation, or 2 coils placed one on either side and stimulated simultaneously, may be superior to unilateral stimulation, and this suggestion should be empirically examined. We also did not see a differential effect of rTMS on obsessions and compulsions when the trends for change in the 2 subscales were directly compared, a finding that is consistent with the effect of other physical treatments on OCD.[1,12,13]

In conclusion, our study suggests that prefrontal rTMS may be an effective treatment for OCD, with an equal proportion of patients benefiting from either right- or left-sided stimulation. This finding needs to be replicated in future studies, but the implications for placebo-controlled studies must be appreciated. Since OCD patients commonly have comorbid depression, and depression appears to respond to left prefrontal cortical stimulation,[2] an argument can be presented for left-sided simulation for future controlled studies of OCD as well. However, comorbid or secondary depression may not have the same response

characteristics as primary depression. The field therefore remains open for further exploratory studies. As stated earlier, studies of rTMS in OCD should also examine the effect of bilateral prefrontal cortical stimulation. Combining such treatment studies with functional neuroimaging may help us understand the physiologic mechanisms involved in the change that occurs.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), atenolol (Tenormin and others), citalopram (Celexa), clonazepam (Klonopin and others), fluoxetine (Prozac), fluvoxamine (Luvox), omeprazole (Prilosec), risperidone (Risperdal), sertraline (Zoloft).

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