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A randomized double-blinded sham-controlled trial of α electroencephalogram-guided transcranial magnetic stimulation for obsessive-compulsive disorder

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Keywords: obsessive-compulsive disorder; anxiety; depression; repetitive transcranial magnetic stimulation; electroencephalogram; randomized controlled trial

Background Obsessive-compulsive disorder (OCD) is a highly prevalent and devastating psychiatric condition. Repetitive transcranial magnetic stimulation (rTMS) is a potential and non-invasive treatment for OCD. Diverse efficacies of rTMS have been reported in different locations or frequencies of the stimulation. The main objective of this study was to assess the treatment effect for OCD with alpha electroencephalogram (αEEG)-guided TMS over dorsal lateral prefrontal cortex bilaterally.

Methods There were 25 OCD patients in the αTMS treatment group and 21 OCD patients in the sham control group. Each subject received 10 daily treatment sessions (5 days a week). The αTMS group had significant reduction in scores of Yale-Brown Obsessive Compulsive Scale and Hamilton Rating Scale for Anxiety (HAMA) compared with the control group at the end of 2-week treatment and 1-week follow-up. Analysis of variance with repeated measures was used to test the effects between the two groups.

Results Significant difference in scores of obsession and HAMA were found between the two groups after treatment. No significant difference in scores of Hamilton Rating Scale for Depression was found between the two groups after the treatment, but statistical significance was shown at the end of 1-week follow-up.

Conclusions αEEG-guided TMS may be an effective treatment for OCD and related anxiety. Delayed response to αTMS in depression suggests that it might be secondary to the improvement of primary response in OCD and anxiety.

Obsessive-compulsive disorder (OCD) is a highly prevalent and devastating psychiatric condition characterized by obsessions and compulsions. Typical symptoms include persistent and recurrent thoughts or mental images and compulsions in the form of repetitive behaviors or mental acts. The patients usually recognize that obsessions are a product of their own mind and try to ignore or neutralize them by compulsions, replacing them with another thought or action. OCD can seriously disrupt normal daily routine leading to a low quality of life, social impairment, and continuous mental distress. A cross-sectional nationwide epidemiological study of the Iranian population aged 18 and older showed the prevalence of OCD in Iran is 1.8% (0.7% and 2.8% in male and female, respectively). In addition to the cognitive-behavioral therapy, medication of selective serotonin reuptake inhibitors (SSRIs) is among the few clinical choices of treatment for OCD. Controlled studies have shown, however, approximately 60% of patients with OCD do not have satisfactory outcomes with SSRI. Many patients have experienced unpleasant adverse effects including difficulty in urination, drop in blood pressure, dry mouth, drowsiness, nausea, headache, and dizziness. It is thus important to find a more effective and safer treatment for OCD.

Repetitive transcranial magnetic stimulation (rTMS) is a novel and non-invasive treatment for various mental disorders. A few studies have suggested that rTMS might help improve the symptom in OCD patients. Patients receiving 3 weeks of daily treatment with low-frequency rTMS over the supplementary motor area (SMA) showed some degrees of symptom improvement in OCD. Others, however, failed to show any significant effect on OCD when high-frequency rTMS was applied over the right prefrontal lobe. There was evidence that abnormal brain electric activities may have played important roles in various mental disorders, such as schizophrenia, OCD, and major depressive disorder. For example, the alpha activity of electroencephalogram (EEG) was found lowered or altered in patients with schizophrenia. Jin et al found

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that, in comparison with the nonresponders, patients who clinically responded to clozapine had a significantly greater increase in alpha EEG photic driving. The degrees of increase in EEG was positively correlated with patients’ clinical improvement. Based on these findings, Jin and colleagues proposed to use a personalized rTMS set at the individual’s intrinsic frequency of αEEG to treat patients with schizophrenia, known as αEEG-guided transcranial magnetic stimulation (αTMS). Abnormal EEGs have also been observed in patients with OCD. The alpha wave amplitude, frequency, and stability were found to be abnormal in prefrontal and temporal lobes in OCD. A study showed that mean frequency of background activity was significantly lower in OCD patients, predominantly for the frontal electrode positions. Modal alpha frequency and maximal alpha frequency were reduced in the frontal regions in OCD patients, and spectral edge frequency and spectral mobility in left and right frontal regions (MOLF and MORF) were both lower. Speer’s study found opposite effects of high- and low-frequency rTMS on regional brain activity in depressed patients. High-frequency rTMS over the left prefrontal cortex was associated only with increases in regional cerebral blood flow (rCBF). Low frequency was 1–5 Hz while 10–20 Hz was high frequency. Thus TMS at the alpha frequency ranged (8 to 12 Hz) in OCD patients may increase rCBF and cortical activity. Based on the rationale that αTMS can be used for schizophrenia, it is speculated that the same treatment may be equally effective in treating patients with OCD. The main objective of this study is to assess the treatment effect on OCD with αEEG-guided TMS over dorsal lateral prefrontal cortex bilaterally.

**METHODS**

**Subjects**

This study was conducted at the Institute of Mental Health in Peking University and Beijing Hui Long Guan Hospital in China. Fifty-two patients with DSM-IV diagnosed as moderate to severe (Yale-Brown Obsessive Compulsive Scale (YBOCS) score of 16 or above) OCD were recruited and enrolled in this double blind and sham controlled study. While 46 patients completed the study 4 (2 from each group) withdrew after two and three treatments. Of the 46 patients, 9 were inpatients and 37 outpatients. All subjects had signed informed consent before participating in the study.

Baseline EEG was recorded for each subject at rest with eyes closed using Cadwell EZ-II acquisition system. Impedance for each electrode was set at 5 kOhm or less. A band-pass analog frequency filter was set between 0.5 and 35.0 Hz and the amplified signals were digitized at 200 points per second and stored on a computer hard disk for off-line analysis. Raw data were visually inspected by a trained technologist to remove artifact-contaminated epochs and calculated with a routine fast Fourier transform with a 1 024 point FFT window to yield a power spectrum for each electrode. The intrinsic alpha frequency was defined as a peak frequency in the alpha band (8–12 Hz). The stimulus rate was determined as an average peak frequency of five frontal leads (F7, F3, Fz, F4, and F8). Using the simple randomization method, enrolled subjects were randomly assigned to αTMS treatment group (n=25) or sham control group (n=21) according to a computer-generated random table by the project manager. The project manager concealed the random table, so the patients, the therapists, and the raters did not know the grouping. αTMS was delivered through a 9 cm circular stimulator (Cadwell High Speed MES-10, USA). The target brain areas were bilateral DLPFC. A 9 cm circular coil was placed either over the midfrontal area with the side edges reaching F3 and F4 or midparietal area with the side edges reaching P3 and P4 of the EEG electrode locations.

| Table 1. Socio-demographic and clinical characteristics of the sample (n=46) |
|---------------------------|-----------------|-----------------|-----------------|-----------------|
| Variables                  | Treatment (n=25) | Control (n=21) | P values        |
| Age (mean (SD))            | 27.12 (8.97)     | 29.86 (9.42)    | 1.007           |
| Education year (mean (SD)) | 12.48 (3.14)     | 14.71 (2.88)    | 2.496           |
| Duration of illness (mean (SD)) | 11.40 (5.65)  | 13.48 (5.34)    | 2.265           |
| Onset (mean (SD))          | 15.72 (6.25)     | 16.38 (6.98)    | 0.260           |
| First professional treatment age (mean (SD)) | 21.80 (10.34)   | 25.24 (11.05)   | 0.067           |
| Gender (n (%))              | Male 17 (0.68)   | 13 (0.62)       | 0.187           |
|                            | Female 8 (0.32)  | 8 (0.38)        | 0.665           |
| YBOCS total baseline        | 25.4 (6.2)       | 23.4 (5.7)      | 1.138           |
| HRSD baseline               | 12.8 (5.5)       | 12 (6.4)        | 0.480           |
| HAMA baseline               | 15 (5.9)         | 12.1 (3.9)      | 1.88            |
frequency was determined according to the patient’s average intrinsic αEEG frequency. Single magnetic pulses were used alternately over the motor cortices to detect the motor threshold (MT), which was defined as visible thumb twitch as response to the lowest intensity of TMS pulse. Treatment stimulus pulse intensity was determined as 80% of an individual’s MT.26

αTMS treatments were given daily, five sessions a week for two consecutive weeks. Each session lasted 20 minutes; each minute included 4 seconds of active stimulation and 56 seconds of rest. For the control group, an unplugged sham coil was placed on the same area of subject’s head while an active coil driven by the same treatment parameters was placed behind and 60 cm away from the subject to simulate the acoustic effect. The total number of magnetic pulses received by each patient varied between 648 and 872 per treatment session according to his/her intrinsic αEEG frequency.

Clinical evaluation was performed by a research psychiatrist at the baseline, after the 5th and 10th sessions of treatment, and 1 week after completing the entire treatment. The assessment instruments used included the YBOCS, Hamilton Rating Scale for Depression (HRSD), HAMA, and Clinical Global Impressions Scale (CGI). The clinicians did not talk to the patients about the therapy. So the patients did not know the group. Both study subjects and clinician were blind to the treatment condition.

Statistical analysis
Statistical analysis was performed with SPSS 13.0 statistical software package (SPSS Inc., USA). Continuous variables are presented as mean ± standard deviation (SD) and categorical variables as frequency (%). Continuous and categorical variables were compared between groups by analysis of independent-samples t-test and Chi-square analysis (Fisher exact test was calculated when needed), respectively. Effect of αTMS therapy across time, as measured by each of the four scales (YBOCS, HRSD-17, HAMA-14, and CGI-S) individually, was separately assessed using analysis of variance (ANOVA) with repeated measures referenced on the sham control group. Greenhouse–Geisser adjustment for degree of freedom was used when the criterion for variance sphericity was not satisfied. Treatment and time interaction effect at weeks 1, 2, and 3 were evaluated referenced on baseline relevant scale scores for each scale, respectively. A P <0.05 was considered statistically significant, and all reported P values were two-sided.

RESULTS
During the treatment, five patients who were treated with αTMS reported mild headache, while four receiving sham also reported mild headache. Symptom appeared in 0.5–1.0 hour following the treatment, which sited in parietal or frontal area, and relieved in 2–3 hours automatically. Four patients reported to feel weak or fatigue shortly after the treatment, which alleviated 2–3 hours later without intervention. No seizures, cognitive difficulties, or other severe adverse effects were found.

The demographic and clinical characteristics of the study sample are displayed in Table 1. There was no significant group difference in age, gender, education level, age of onset, and duration of illness.

Baseline severity of symptoms as measured by YBOCS, HRSD, HAMA, and CGI were not significantly different between active and sham groups (Table 2). ANOVA of YBOCS score with repeated measure of time revealed a significant effect of time (F=49.32, P <0.01) and an interaction of treatment by time (F=7.30, P <0.01). The result showed that the group difference in treatment-by-time interaction starts at week 2 of the treatment (F=17.89, P <0.01) and remained to be significant at the end of 1-week follow-up (F=8.84, P <0.01, Table 3).

The sub-scores of obsession showed significant effects of time (F=7.64, P <0.01) and treatment-by-time interactions (F=47.32, P <0.01). The result showed the group difference in treatment-by-time interaction after 2-week treatment (F=15.85, P <0.01), and at the end of 1-week follow-up (F=6.30, P <0.05) (Table 3).

The sub-scores of compulsion showed significant effects of time (F=13.06, P <0.01) and treatment-by-time interactions (F=1.67, P >0.05). But there were no differences between the two groups (Table 3).

The scores of HAMA showed significant effects of time (F=24.53, P <0.01) and treatment-by-time interactions (F=4.06, P <0.05). Similar to the YBOCS, significant group differences of each time point of treatment-by-time interactions were found at 2-week treatment (F=9.94, P <0.01) and at the end of 1 week follow-up (F=4.58, P <0.05, Table 3).

The repeated measures ANOVA with Greenhouse–Geisser adjustment revealed a group-by-time interaction in HRSD (F=3.50, P <0.05), and the HRSD scores showed no significance between the two groups either after 1-week (F=0.44, P >0.05) or 2-week treatment (F=2.22, P >0.05). However, it was statistically significant at the end of 1-week follow-up (F=5.24, P <0.05, Table 3).

The result showed that there were changes in scores of YBOCS, HRSD, and HAMA over time following both αTMS and sham treatments. However, the significant main effect interaction of treatment-by-time suggested more symptom reduction in the αTMS group than the control group in YBOCS and YBOCS (obession).

The subject is considered to respond to treatment when CGI score is 1 or 2 and ≥35% reduction in YBOCS score, and be in remission when the YBOCS score is <16.27 Nine subjects in the αTMS group and none in the control
group showed remission ($\chi^2=1.62, P>0.05$) in the 1-week follow-up after treatment. Neither tests were statistically significant ($P>0.05$) between the groups.

**DISCUSSION**

This study demonstrates that $\alpha$TMS over dorsolateral prefrontal cortex bilaterally could not improve response to drug treatment for OCD patients in 2-week treatment. Although placebo effects were possible, the study shows that the obsession improved in 2-week treatment. It seems that $\alpha$TMS has clinical effect on symptoms of obsession but not on compulsion. The clinical effect on obsession did not show until the second week of treatment and sustained into the third week after the treatment had been completed. It is thus reasonable to hypothesize that longer treatment may have more robust effect on OCD.

So far, the pathogenesis of OCD has remained unclear. Neurophysiological, neuroimaging, and electrophysiological studies exploring functional and structural abnormality in the cerebral orbital–frontal edge–basal ganglia loop had shown decreased cortical subcortical neurons inhibition function in the patients of OCD. Single-pulse TMS was first used to stimulate the right prefrontal cortex in patients with OCD. It showed that the obsession improved in 2-week treatment. It seems unclear whether $\alpha$TMS could produce more robust effect on OCD.

A study
conducted by Prasko et al showed that rTMS with the frequency of 1 Hz at 110% of MT over the left dorsolateral prefrontal cortex for 2-week treatment had no effect in OCD patients.  

In this study, a new treatment has been attempted. αTMS is proved for the first time to be effective on the symptoms of OCD. We believe that the effect was brought about by an effective EEG tuning in the alpha frequency (details will be discussed in a separate report on the EEG effect and its relationship with the change in clinical symptoms). It could also change the binding force of neurotransmitter receptors and blood flow of brain. Another possible mechanism of action may be involved in the stimulation of motor cortex. A study found OCD patients had greater relative activation of the SMA and deactivation of the rostral anterior cingulate during high versus low-conflict (incongruent > congruent) trials. It may be a compensatory response to a neuronal abnormality in the region. Kumar and Chadda showed that low-frequency rTMS of the SMA appeared to be a promising treatment strategy as an add-on treatment for patients with treatment-refractory OCD.

It was noteworthy that comorbid symptoms of anxiety and depression are also improved in the OCD patients during the trial. This result is supported in part by the findings from other studies. The same pattern of change between OCD and anxiety suggests a direct relationship between the two clinical symptoms. The delayed improvement in depressive symptoms, however, suggests a different relationship, where reduction of depression may be secondary to the improvement of primary symptom of OCD. Lack of immediate effect on depression may also be explained by different stimulus parameters. Many studies had shown anti-depressive effect by stimulation of the left dorsolateral prefrontal lobes with high frequency (5–20 Hz) or the right dorsolateral prefrontal lobes with low frequency (≤1 Hz). Sarkhel et al failed to show that adjunctive high-frequency right prefrontal rTMS had any effect in OCD. However, they reported a modest effect in the treatment of comorbid depressive symptoms in patients with OCD. Ruffini et al’s study showed that low-frequency rTMS of the left OFC produced significant but time-limited improvement in OCD patients compared to sham. In the present study, the clinical efficacy of αTMS of the bilateral dorsolateral prefrontal cortex on OCD may reflect not only the effect of individualized stimulus rate but also the diffuse stimulus location. Therefore it shows inconsistent efficacy with other studies.

By the end of 1-week follow-up in this study, 52% patients in the αTMS treatment group remained clinically stable. It suggests some degree of durability of αTMS in OCD and a longer follow-up is needed to further explore the long-term effect.

The uncontrolled medication treatment might have confounded this study results. Several patients were medication-free during the study while others received concomitant treatment of different types of SSRIs at different dosages. The complex interaction between the antidepressants and rTMS may significantly alter the clinical outcome. It is thus necessary to replicate the study with better control conditions in a larger sample size.

In conclusion, αTMS is a non-invasive treatment which could improve the obsessive, depressive, and anxiety symptoms effectively in OCD patients. And αTMS could adjust the OCD patient’s abnormal brain electrical activity resulting in improving obsession. The study provides a new attempt to treat OCD. Large sample, randomized controlled trial should be conducted to explore the efficacy for OCD.

Treatment-refractory OCD patients. We believe that the effect was brought about by an effective EEG tuning in the alpha frequency (details will be discussed in a separate report on the EEG effect and its relationship with the change in clinical symptoms). It could also change the binding force of neurotransmitter receptors and blood flow of brain. Another possible mechanism of action may be involved in the stimulation of motor cortex. A study found OCD patients had greater relative activation of the SMA and deactivation of the rostral anterior cingulate during high versus low-conflict (incongruent > congruent) trials. It may be a compensatory response to a neuronal abnormality in the region. Kumar and Chadda showed that low-frequency rTMS of the SMA appeared to be a promising treatment strategy as an add-on treatment for patients with treatment-refractory OCD.

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Neuroimaging studies are also needed to explore the change in the brain of OCD patients by treatment of αTMS.

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