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Alpha EEG guided TMS in schizophrenia

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Background
Alpha EEG guided Transcranial Magnetic Stimulation (αTMS) of the dorsolateral prefrontal cortex (DLPFC) has shown promising efficacy for treating the negative symptoms of schizophrenia.

Objective/ Hypothesis
The purpose of the current investigation was to test (1) the therapeutic effect in other domains of symptoms of schizophrenia and (2) the specificity of stimulus location. The hypothesis to be tested was that global alpha EEG normalization after αTMS would help improve the clinical symptoms of schizophrenia, regardless of the site of stimulation.

Method
Seventy-eight patients with schizophrenia were enrolled in a randomized, double-blind, sham-controlled study with four study groups: frontal αTMS, parietal αTMS, frontal sham, and parietal sham. Patients received daily treatment for 10 days and clinical evaluations at day 5 and 10. The stimulus rate and intensity were determined by individual's characteristic alpha frequency and motor threshold (80%).

Results
Positive and general psychotic symptoms improved significantly after αTMS ($P < 0.02$). Frontal and parietal αTMS had similar effects ($P = 0.48$). (3) αTMS with concomitant typical neuroleptics treatment had greater efficacy than atypical neuroleptics ($P < 0.04$). Degree of EEG normalization as measured by increase in Q factor was highly associated with the improvement in all three domains of symptoms of schizophrenia ($P < 0.04$).

The study was sponsored by the Stanley Medical Research Institute treatment grant to Y.J. (ID: 03T-354). Data have been presented in poster format at the 4th Annual Conference of the International Society for CNS Clinical Trials and Methodology (ISCTM) and at the 1st Schizophrenia International Research Society Conference.

Dr. Yi Jin holds patents regarding the use of EEG-guided rTMS, including the methods described in the current study, and has a financial interest in NeoSync, a private company exploring the commercial viability of such. Nonetheless, neither of these factors was concurrent with the time of data collection or analysis for any of the results reported in the current report. In addition, Dr. Jin and Dr. Trung Thai are currently employed at The Brain Treatment Center, which offers a type of EEG-guided rTMS treatment, analogous to that described herein. However, at the time of data collection and analysis, all were employed at the University of California, Irvine Neuropsychiatric Center, which offers no such treatment modality (then or now). None of the other authors report any financial disclosures that could present a potential conflict of interest with the current results.

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Conclusions
Alpha EEG normalization after treatment with αTMS may directly subserve the processes underlying clinical improvements in schizophrenia. Nonetheless, given the confound of possible unblinding of participants because of an inactive sham control, the current results should be considered preliminary until replicated further.

Keywords alpha EEG; TMS; schizophrenia

Since it was first reported by Barker et al.,[1] most studies investigating the clinical application of repetitive transcranial magnetic stimulation (rTMS) have primarily focused on the treatment of major depressive disorder.[2] Recently, however, an increasing number of studies have been conducted to explore its therapeutic potential for other neuropsychiatric disorders,[3-6] including schizophrenia.[7-9] It is generally believed that rTMS at low frequency (< 1 Hz) inhibits cortical excitability[10] and high frequency (>1 Hz) reduces intracortical inhibition[11] and promotes long-term plastic effects.[12] Early studies[13] using brief, single-pulse TMS have shown some benefits for schizophrenia patients but were limited to improvements in mood. On the basis of the early neural imaging findings of auditory hallucination with hyperactivity in auditory cortex,[14,15] Hoffman et al.[16] reported a series of investigations using low-frequency rTMS over the left temporoparietal area in treating patients with active auditory hallucinations. They found that patients who received active rTMS had significant reduction of auditory hallucinations in both intensity and frequency as compared with a sham-controlled group. Others, however, have failed to replicate these findings.[17]

In contrast to the pathophysiologic mechanism of auditory hallucinations, growing evidence has shown that the negative symptoms of chronic schizophrenia are related to decreased cortical activation. Cerebral volume is often found to be reduced in temporal and frontal cortexes. Neural imaging studies in schizophrenia suggest reduced and/or anomalous activation of the cortex, primarily the frontal cortex. Decreased levels of dopamine metabolites have been reported in patients with schizophrenia with poor prognosis and moderately severe social impairment.[18] Following this line of thought, there has been increasing interest in using high-frequency rTMS to enhance activation of the prefrontal cortex to treat negative symptoms in schizophrenia.[19] Open label studies of high-frequency rTMS (10-20 Hz, given for 1-4 weeks) of the left dorsolateral prefrontal cortex (DLPFC) have shown beneficial effects on patients with prominent negative symptoms.[20] Similar to the rTMS studies on auditory hallucination, results on negative symptoms been somewhat inconsistent among different laboratories.[21] Differences in rTMS parameter selection may have played a significant role in the inconsistency of study results.

In an attempt to standardize the procedure with respect to the variation of patients' electrophysiologic characteristics, Jin et al.[9] proposed the use of an individualized rTMS treatment protocol, where stimulus rate is determined according to the subject's intrinsic alpha EEG frequency (αTMS).[9] Patients with schizophrenia often have reduced alpha activity (power and coherence)[22] and their clinical improvement after antipsychotic treatment has been found to correlate with the degree of alpha EEG normalization.[23] The frequency of alpha EEG oscillation at its normal condition has been found to be stable[24,25] and has strong resonant properties. In a linear resonant system, pulses applied at approximately the natural frequency produce maximum oscillation amplitude at 90 degrees phase difference to the applied pulses.[26] At these resonant frequencies, even small periodic driving forces can produce large amplitude oscillations. Accordingly, it has been hypothesized that the stimulus rate of rTMS set individually at each patient's intrinsic peak alpha frequency would induce a resonant EEG response to enhance synchronization and consequently, reduce the clinical symptoms. A previous study[9] showed that αTMS of bilateral DLPFC had significantly greater therapeutic effect on the negative symptoms as compared with sham, 3 Hz, and 20 Hz rTMS. This finding was supported by a corresponding change in the α EEG. The current study was designed to answer the remaining questions in the first study: (1) Is α EEG equally effective on positive symptoms in schizophrenia? (2) Is the stimulus location of DLPFC specific for schizophrenia treatment? (3) What is the concomitant effect with neuroleptic treatment? (4) Can EEG normalization predict symptomatic change?

Methods

The project used parallel groups in a randomized, double-blind, sham-controlled design. The complete randomization was used with a random table. Possible imbalance of other variables was considered to covariate for the final analyses. The study was carried out at the outpatient clinics of the University of California, Irvine, Neuropsychiatric Center (UCINC) and Beijing Institute of Mental Health, Peking University (PUIMH). The study protocol and informed consent were reviewed and approved by both institutional review boards at UCINC and PUIMH. Interrater reliability on diagnosis and evaluation instruments between the institutes and individuals were tested using six prerecorded psychiatric interviews in three diagnostic categories, namely,

schizophrenia, major depression, and normal control. High agreement was reached among all four research psychiatrists with kappa value > 0.76.

Subjects

Seventy-eight patients diagnosed with schizophrenia (age: 37.3 $\pm$14.0 years old; sex: 45 males, 33 females; duration of illness: 15.4 $\pm$ 11.6 years) who had been stabilized on current antipsychotic medications for at least 30 days were enrolled in the study. Each patient received a structured interview with two research psychiatrists and met the DSM-IV diagnostic criteria for schizophrenia or schizoaffective disorder. Severity of symptoms was evaluated by the Positive and Negative Syndrome Scale (PANSS). As an inclusion criterion, a minimum of 65 on the total PANSS score was required at baseline. Patients who met any of the following criteria were excluded: significant physical illness in the 4-week period preceding the start of the study, current diagnosis or past history of epilepsy, major head trauma, progressive neurologic diseases, high-dose ($>$ 400 mg) clozapine in the past 3 months, electroconvulsive treatment in history, present history of any other psychiatric diagnosis, drug dependence, or toxic psychosis in the preceding 8 weeks. Each patient provided fully informed written consent before participation in any study procedures.

Procedure

Each patient admitted to the study was randomly assigned into one of the four study groups based on stimulus location (bilateral frontal [BF] and bilateral parietal [BP]) and treatment (αTMS and sham). The sample size ratio of BF/BP was one, and αTMS/sham, was two, considering the high variance of change scores in the treatment group than sham. Patients were kept blind to the treatment condition and unaware of the difference of stimulus location. Each treatment consisted of 10 daily sessions during a 2-week period. Patients' current antipsychotic treatments were kept unchanged during the study. In each daily treatment session, a CADWELL 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. Stimulation was given 4 seconds per minute for 20 consecutive minutes per session at an intensity of 80% motor threshold, a minimal magnetic pulse (biphasic) that reliably induced visible contra lateral thumb movement (average intensity: 142 joules per pulse). In the current study, only right motor cortex was stimulated to identify motor threshold. The rate of active stimulation was individualized according to the alpha EEG intrinsic frequency (8-13 Hz) with an accuracy level of 10% of a hertz. It was determined on each patient's average alpha peak frequency obtained from three central EEG leads (C3, C4, and Cz). The central leads alpha activity tends to have the frequency characteristics of both anterior and posterior waves because of the volume conduction. Enhancing the common frequency of the different cerebral regions has better chance to facilitate the coherence between them. In the current study, however, no specific effort was made to qualitatively differentiate the waveforms between Mu and alpha rhythms. Sham stimulation was given by applying an unplugged coil to the same frontal or parietal locations and an activated coil left 2 feet away behind the patient to mimic the acoustic effect of active stimulation. We were informed by the manufacture that approximately 25% peak magnetic flux would penetrate the scull at a 90-degree tilted position of an active coil, which was not acceptable in the current study because it might induce well an EEG resonant response.

EEG was recorded from each subject in a supine position with their eyes closed throughout the testing period. Nineteen EEG electrodes (Ag-Ag Cl) were used according to the International 10-20 system and referenced to linked mastoids. EOG leads were placed 1 cm below and above each outer canthus to record eye movement. The impedance of each electrode was lower than 5 KΩ. Four minutes of EEG epochs were collected and digitized by a 12-bit A/D (analog/digital) converter at the rate of 200 Hz by a Cadwell EZ II acquisition system. Raw EEG data were edited offline by an experienced technician who was blind to the treatment conditions to eliminate epochs contaminated with significant ($> 3^\circ$ arc) eye movements or any other type of apparent artifact. Approximately 2 minute data from each channel were calculated by a fast Fourier transform (FFT) routine using a 2048 data point Hanning window to produce a power spectrum with 0.1 Hz frequency resolution, through which four consecutive EEG bands (δ: 0.5-4.0 Hz, θ: 4.1-7.9 Hz, α: 8.0-13.0 Hz, and β: 13:1-30.0 Hz) were yielded. The FFT window was weighted with a –18 dB sidelope roll off to minimize the spectral leakage. Peak frequency and power density of each band were automatically calculated.

Severity of psychosis, depression, and movement symptoms were assessed with PANSS, Montgomery-Asberg Depression Rating Scale (MADRS), Barnes Akathisia Rating Scale (BARS), and Simpson-Angus Scale (SAS), respectively. All rating scales and EEGs were administered at screening, baseline (immediately before first treatment), and after the fifth and 10th treatments. The technicians who administered the αTMS procedures were not blind to the treatment condition, but the evaluating physicians and EEG technicians remained unaware of the type of treatment throughout the duration of study. A priori categoric definition for clinical response was $>$ 30% baseline-to-post treatment reduction at the end of treatment on PANSS scores.

Statistical analyses

Patients with a baseline and at least one additional set of completed assessments (at least five treatment sessions) were included in the analysis of mean treatment effect. Efficacy in clinical ratings was evaluated by using analyses

of variance (ANOVA) with repeated measure over time. The models included two between-subject factors of treatment and location, and one within-subject factor of time. Effect of concomitant antipsychotic treatment was tested based on the categorization of typical and atypical neuroleptic medications. Grouping differences of all other measures were tested individually using the same statistical model with one between factor of treatment and one within factor of evaluation time point, assuming the variance between study sites are homogeneous. Covariance for the baseline was used when variance at baseline was found different between groups. The Kruskal-Wallis test was used for post hoc comparisons of clinical responsive among treatment groups. Using a predefined response criterion, a contingent table analysis was also used to test the group difference in responding rate.

EEG variables used in the analysis included power density (Pwr), peak frequency (Fp), Fp longitudinal coherence, and frequency selectivity (Q).[25] Data for power density in all four frequency bands and nineteen channels were reduced by averaging the nearest leads in the corresponding brain areas,[26] namely, Frontal (F7, F3, F4, and F8), Temporal (T3, T5, T4, and T6), and Parietal-occipital (P3, P4, O1, and O2). Coherence analysis was carried out between Fz and Pz in the peak alpha frequency. Recording from Cz was chosen to calculate the Q factor (peak frequency/half-power bandwidth), a measure of the alpha frequency selectivity (Figure 1). It was measured in the frequency domain by using a 60-second artifact-free EEG epoch and a 2048 data point FFT with a 10-point smoothing procedure. Multivariate analysis of variance (MANOVA) across all channels for each variable was performed to test the treatment and stimulus location effects. Change score for each variable before and after αTMS was used to correlate with the change score of each clinical measure from the same time points.

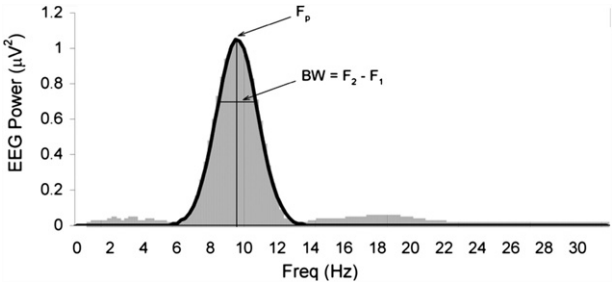

Figure 1 Calculation of Q factor of resting alpha EEG. It measures the degree of energy decay per cycle during a damped oscillation. The greater the Q is, the slower the decay in the oscillation envelope would be. FFT with 10-s window was first used to calculate the spectrum followed by a 10-point smoothing procedure to normalize the distribution (shaded area). Profile (solid line) is a curve-fitted Gaussian function used to calculate peak frequency (Fp) and quality factor (Q = Fp/BW). BW = F2 − F1 is half-power bandwidth at 3 db roll-off of the peak magnitude.

Results

Fourteen subjects dropped out of the trial before the completion of the first five sessions of treatments, of which one had an exacerbation of psychotic symptoms and the rest were due to noncompliance and family relocation. Nine patients experienced mild tension headache during the first week of treatment. No other severe side effects were reported from the subjects during the period of study. A total of 64 patients completed clinical measures and the second week EEG. Forty-one of them were from the frontal or parietal αTMS groups and the remaining 23 were from Sham group.

αTMS effects on EEG

There were no group differences between the frontal and parietal treatment groups in baseline power density (Huynh-Feldt adjustment: $F = 0.55$, df = 2.564,158.940, $P = 0.62$), frontoparietal (F-P) coherence ($F = 0.04$, df = 1.63, $P = 0.85$), or Q factor ($F = 0.16$, df = 1.63, $P = 0.69$). The following analyses were performed based on the percentage change scores that were calculated as (posttreatment – baseline)/baseline.

Power density: MANOVA with repeated measures of recording channel and frequency band showed no overall effect of treatment ($F = 2.8$, df = 1.63, $P = 0.21$) or main effect interaction among treatment, frequency band, and brain area (Huynh-Feldt adjustment: $F = 1.68$, df = 1.088, 67.434, $P = 0.20$). Specifically, there is no difference in alpha power change as measured by wide band (8-12 Hz) energy density between TMS and Sham group ($F = 0.91$, df = 1.63, $P = 0.34$).

Frontoparietal (F-P) coherence: Patients with αTMS had significantly greater improvement than those in Sham in the alpha peak frequency coherence between midfrontal and parietal areas ($F = 5.41$, df = 1.63, $P = 0.02$; Figure 2).

Alpha frequency selectivity: αTMS group had significantly greater increase in Q factor after the 2 weeks of treatment than Sham group ($F = 7.55$, df = 1.63, $P = 0$; Figure 3).

αTMS effects on symptoms of schizophrenia

αTMS effects on the three domains of symptoms of schizophrenia measured by the PANSS (positive symptoms, negative symptoms, and total scores) were calculated as percentage change scores [(baseline – posttreatment) / baseline] at the end of fifth and tenth sessions of treatment. Overall effects and main effect interactions of all three measures at the two time points were tested using multivariant analysis of variance (MANOVA) with repeated measure over time. No statistical significance was found for the difference between the two sham groups ($F = 0.12$, df = 1.30, $P = 0.72$) or between the two αTMS groups ($F = 0.51$, df = 1.55, $P = 0.48$). Therefore, data within each treatment at frontal

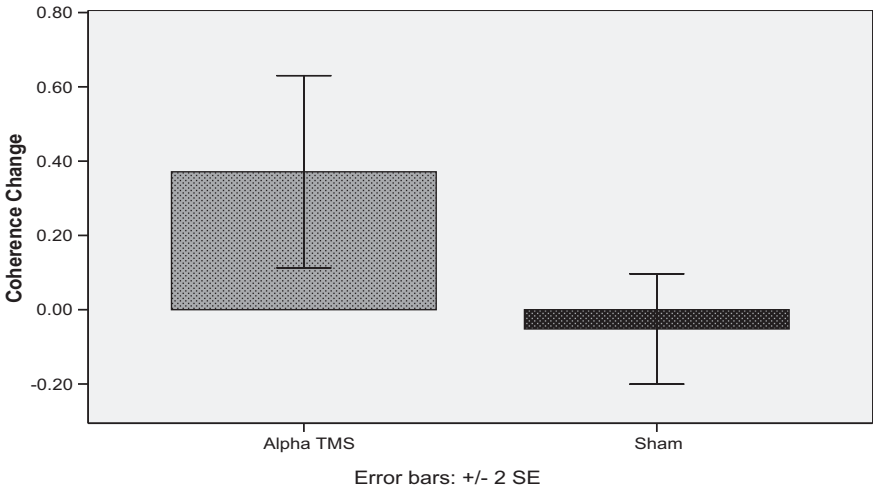

Figure 2 Changes in longitudinal (Fz-Pz) coherence at the peak alpha frequency. Y axis indicates the changes score [(end of study – baseline) / baseline].

and parietal locations were combined into two new groups, sham and αTMS, for further analyses.

Repeated MANOVA showed no main effect interaction among measure, treatment, and study site ($F = 0.60$, df = 4.166, $P = 0.66$), suggesting that the patterns of clinical response to the TMS and sham treatments were not different between UCINC and PUIMH. Overall treatment effect, however, was statistically significant ($F = 4.43$, df = 1.63, $P = 0.04$) with main effect interaction among clinical measure, time, and treatment ($F = 4.00$, df = 1.63, $P = 0.05$). Post-hoc tests (Figure 4) revealed that the significant differences between sham and αTMS were in total PANSS score ($F = 5.36$, df = 1.63, $P = 0.02$) and positive symptom score after the 10th session ($F = 7.49$, df = 1.63, $P = 0.01$) but not after the fifth session of treatment ($F < 2.33$, df = 1.63, $P > 0.1$). Same analysis for the total score when covariate for the positive score showed no significant difference between treatment groups ($F = 0.83$, df = 1.63, $P = 0.37$), suggesting that the positive symptom effect contributed to the significant finding in the composite total score. There were no statistically significant changes in the negative symptoms either after the fifth ($F = 0.33$, df = 1.63, $P = 0.57$) or 10th treatment ($F = 0.80$, df = 1.63, $P = 0.37$).

To further test the treatment effect as referenced to clinical significance, percentage change in PANSS score was classified into two categories: cases with $\geq$ 30% improvement were named "responder" and $<$ 30%, "nonresponder." It was found that 17 of 41 patients responded to the αTMS (42%), whereas three of 24 responded to the Sham treatment (12%). Nonparametric analysis showed this difference to be statistically significant ($X^2 = 5.96$, $P = 0.01$).

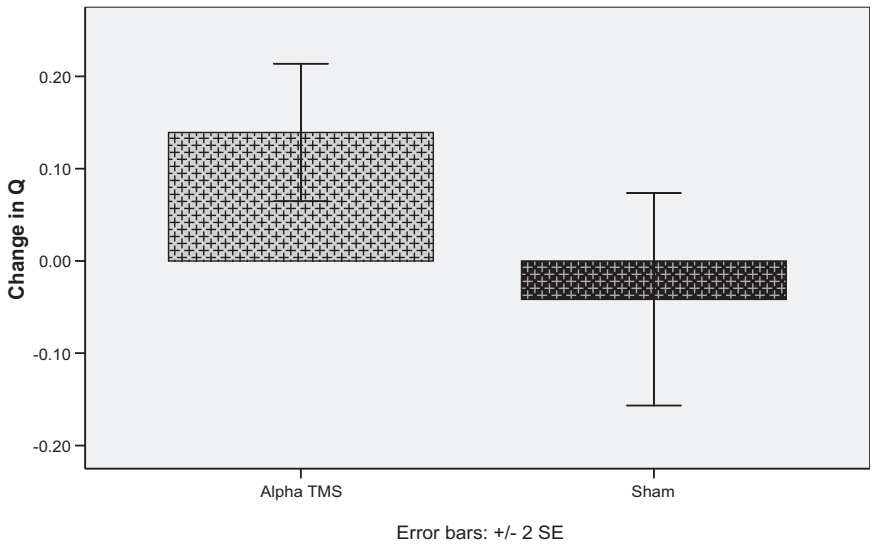

Figure 3 Changes in alpha EEG frequency selectivity (Q factor). Y axis indicates the changes score [(end of study – baseline) / baseline].

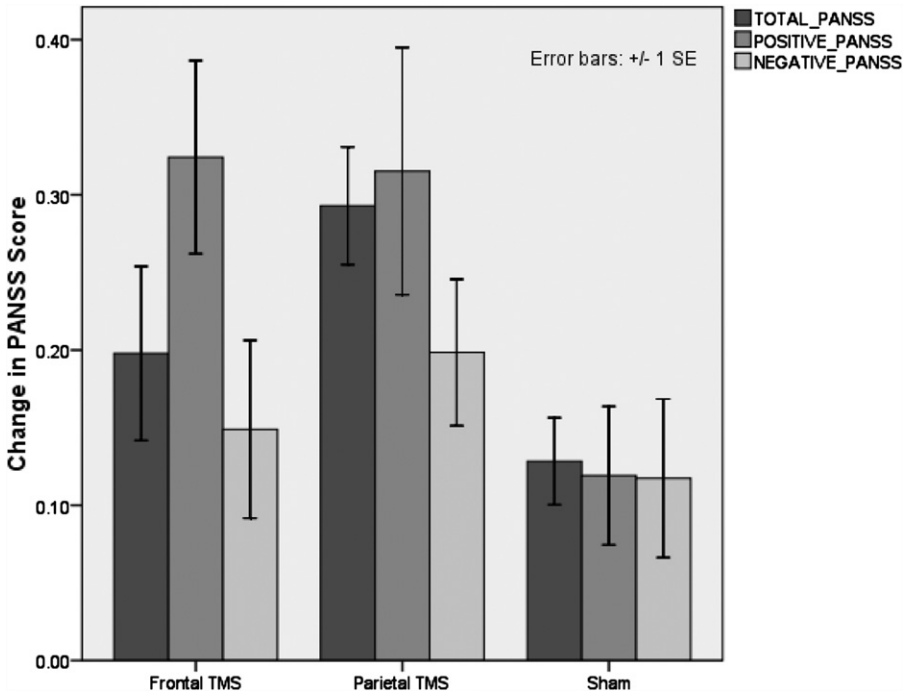

Figure 4 αTMS effect on psychotic symptoms measured by PANSS. Both frontal and parietal active treatment group had significantly greater effect than sham in positive but not in negative symptoms. Total score is a composite measure including positive and negative scores. The treatment effect after αTMS could not hold when the linear effect of positive symptom effect was removed (ANCOVA).

Relationship between changes in clinical symptoms and EEG

Although there were no apparent associations between EEG power densities and clinical changes ($r < 0.15$, $P > 0.25$), significant correlations were found between the increase in F-P alpha coherence and clinical improvement in both positive ($r = 0.30$, $P = 0.02$) and negative symptoms ($r = 0.29$, $P = 0.02$). Increase in Q factor was highly associated with the improvement in both domains of symptoms of schizophrenia (Positive: $r = 0.26$, $P = 0.04$; Negative: $r = 0.27$, $P = 0.03$). Neither change in coherence ($r = 0$, $P = 0.95$) nor Q factor ($r = 0.10$, $P = 0.45$) was associated with the improvement in depressive symptom.

αTMS and concomitant antipsychotic treatment

Of the total 64 cases used in the final analysis, 44 cases had concomitant antipsychotic treatment with either *typical* or *atypical* neuroleptics. The remaining 20 patients received treatment with acupuncture, herbal medicine, or both during the study. Because of the inconsistency of the treatment and difficulty of classification, however, these patients were excluded in this stage of analysis. Patients with *typical* neuroleptic treatment (n = 19) had greater clinical response than those with *atypical* neuroleptic treatment (n = 25) in positive symptoms ($F = 8.18$, df = 1.42, $P = 0.01$). Response in negative symptoms remained the same between the two concomitant treatment groups ($F = 0.16$, df = 1.42, $P = 0.70$).

Effect of gender, age, and duration of illness

There was no overall gender effect on all three measures of psychotic symptoms (ANCOVA: $F < 0.67$, df = 1.43, $P > 0.05$) nor the main effect interaction among measure, time, and gender ($F = 1.10$, df = 2.86, $P = 0.34$). Age and duration of illness were found to be inversely correlated with the degree of improvement in general psychotic symptoms (Age: $r = -0.55$, $P = 0.001$; Illness duration: $r = -0.59$, $P = 0.001$) and positive symptoms (Age: $r = -0.50$, $P = 0.001$; Illness duration: $r = -0.57$, $P = 0.001$), but not with the negative symptoms ($r = -0.16$, $P = 0.32$).

αTMS effect on depression

Depression as measured by Calgary Depression Scale was improved after αTMS ($t = 3.77$, df = 39, $P = 0.001$) but not sham ($t = 1.32$, df = 24, $P = 0.2$). Furthermore, the improvement of depression after αTMS was found to be significantly correlated with the change in the negative symptoms ($r = 0.37$, $P = 0.02$) but not with changes in the general psychotic symptoms ($r = 0.24$, $P = 0.14$) or positive symptoms ($r = 0.07$, $P = 0.65$).

αTMS effect on EPS

After the αTMS, extra pyramidal symptoms (EPS) significantly improved as measured by changes in Abnormal Involuntary Movement Scale ($t_{39} = 2.13$, $P = 0.04$), Extra

Pyramidal Rating Scale ($t_{39} = 2.34$, $P = 0.02$), and Barnes Akathisia Scale ($t_{39} = 3.0$, $P = 0$). In comparison, there were no changes in the same measures after the sham treatment (AIMS: $t = -0.51$, df = 24, $P = 0.62$; ESRS: $t = 0.76$, df = 24, $P = 0.45$; Barnes: $t = -0.79$, df = 24, $P = 0.44$).

Discussion

This project was intended to replicate and extend previous findings supporting the therapeutic efficacy of αTMS on symptoms of schizophrenia[9] with an improved study design. In addition to the randomized and double-blind design, we included a larger sample, four parallel groups, and two study sites. Consistent with our earlier study, the current results have demonstrated that rTMS with the stimulus rate individually set at the subject's intrinsic frequency of alpha EEG is significantly more effective in treating symptoms of schizophrenia as compared with sham control. These effects were independent of the stimulus location; bilateral parietal αTMS was just as effective as bilateral prefrontal stimulation particularly in treating psychotic symptoms. Because of the nature of sham that did not provide an accurate somatosensory simulation, however, there does exist the potential that the participants did not remain blinded to the treatment condition. Therefore, we would consider the study results to be preliminary. Specialized sham coils with proper assessment of blindness should be used in the future studies.

The current clinical finding was supported by the EEG responses to the stimuli showing that neither frontal nor parietal stimulation caused any different changes in alpha power density. Compared with baseline, however, both stimuli increased alpha peak frequency coherence between frontal and parietal areas, and alpha frequency selectivity (Q factor). Contrary to the traditional thelamocortical oscillation model for alpha generation, we believe that the increase in local and longitudinal synchronization in the current study is more likely to be the consequence of corticocortical EEG entrainment induced by the repetitive magnetic stimulation. First of all, the coil used in the study was a large diffuse coil that was capable of producing an extended magnetic field to "drive" neural activity in an area of at least 9 cm in diameter. Secondly, alpha EEG has a strong resonant property; it will respond through the brain's volume conduction to any weak repetitive stimulation as long as the stimulus rate is close enough to its intrinsic frequency. The clinical improvement after the treatment appeared to be associated with these EEG changes, suggesting that the improvement in local and longitudinal alpha EEG synchronization may play an important role in the antipsychotic treatment. This hypothesis requires further test by directly comparing the effect of focal and diffused TMS treatments.

In contrast to the earlier study, however, the current findings did not reveal a similar therapeutic effect on negative symptoms. It is believed that this discrepancy is most likely attributable to differences in the entry-level symptom composites of subjects enrolled in the two studies. The earlier study focused on chronic schizophrenic patients with predominantly negative symptoms. Patients who had moderate or severe positive symptoms were excluded from the study. Patients in the current study, however, were less chronic and more severe in positive symptoms. To ensure the compatibility of the symptom composite between the two studies, we resampled the study subjects according the early study criteria by selecting patients with negative symptom score greater than 20 and positive score less than 19 to match the previous study. Analysis in the small group showed that αTMS was significantly more efficacious than sham for negative symptoms ($F = 4.0$, df = 1.24, $P = 0.05$), which appeared to agree with the previous finding. Since this finding was a result of a post hoc analysis, a dedicated replication study is needed before the conclusion can be drawn.

One of the unexpected findings in this study is that the αTMS, when used with concomitant *typical* neuroleptic treatment, had greater therapeutic effects on symptoms of schizophrenia than when combined with *atypical* neuroleptics. Although the specific mechanism underlying this finding is unknown, it is speculated that it may be attributable to an alpha EEG "ceiling effect" caused by the atypical antipsychotics. An earlier study[23] showed that *atypical* but not *typical* neuroleptic treatment could significantly enhance the alpha EEG power density in patients with chronic schizophrenia. This hypothesis was also tested in the current study using MANOVA. This revealed that alpha EEG power after αTMS with concomitant typical neuroleptic treatment increased significantly more than that with atypical neuroleptic treatment ($F = 3.05$, df = 3.36, $P = 0.04$). However, changes in Q factor and longitudinal coherence did not reach statistical significance between the two concomitant treatment groups. Patients with atypical neuroleptics that remained symptomatic during the study might be more resistant to the "alpha enhancing" TMS because both treatments presumably share a similar mechanism regarding underlying neurophysiologic changes.

As demonstrated by others, the present results support the finding that rTMS treatment has a positive effect on depressive symptoms in patients with schizophrenia. However, the degree of improvement in depression after the treatment was not correlated with the changes in psychotic symptoms. Accordingly, it is believed that the antipsychotic effect of αTMS found in the current study is not reasonably attributable to the same mechanism commonly reported in antidepressive studies of rTMS.

Along with a few other investigators' work, we have previously demonstrated that human alpha EEG plays a critical role in spatial neural coding during normal cognitive processes.[25] Alpha EEG is believed to work as an internal "brain clock" to bind the scattered neural informal in time by providing periodic excitatory cycles. The authors

have also shown that abnormalities of the alpha EEG are often associated with schizophrenia and other mental disorders.[27] The psychotic symptoms often found in schizophrenia are actually altered cognitive phenomena that may be explained in part by the abnormal neural coding during the information process. Thus, it has been hypothesized that the normalization of alpha EEG could be directly involved in the effective treatment of mental disorders characterized by disturbed neurocognitive processes. The current treatment protocol was designed based on the resonant characteristic of EEG oscillation to "enhance" rhythmic alpha activity. If the EEG oscillates coherently in a given frequency band (e.g., alpha), repetitive stimulation near its intrinsic frequency can induce a strong resonant response. Using a novel electromagnetic stimulation procedure, the current results have demonstrated that alpha EEG is indeed "tunable." Although the power density of alpha EEG remained unchanged, the frequency selectivity (Q) and the long-rang coherence at the intrinsic frequency increased significantly after the αTMS treatments, regardless of the site of stimulation. The levels of increase in the alpha Q factor and coherence, but not in power, were further observed to be highly correlated with the degree of clinical improvement. Q factor and coherence measure the degree of neural synchronization in a given frequency at different spatial scales. These findings suggest that it is the temporal and spatial synchronization but not the wide-band power density of alpha EEG that influence the pathophysiology of schizophrenia. As such, the current results are of particular interest because they provide evidence, for the first time, that psychotic symptoms in schizophrenia may be altered by direct manipulation of the alpha EEG. Because of many confounding factors and lack of other frequency controls, more studies are needed to further test this EEG based TMS efficacy.

One of the other important findings in the current study is the therapeutic effect of αTMS on EPS, a common side effect generally attributed to the administration of dopamine blockers. It is believed that two mechanisms are possibly involved in the symptom relief process: (1) increasing dopamine concentration directly in the basal ganglia to compensate for the receptor blockade effect and (2) enhancing the high-frequency oscillatory afferent from the cortex to inhibit the spontaneous low-frequency activity in the basal ganglia. Research in experimental animals suggests that descending pathways from the frontal cortex modulate the release of dopamine in subcortical areas such as the striatum.[28] This occurs through direct glutamatergic corticostriatal projections[29] or by an indirect effect on mesostriatal dopamine neurons in the midbrain.[28] Using [11C]raclopride and positron emission tomography, Strafella et al.[30] have found that rTMS of the left dorsolateral prefrontal cortex caused more reduction in [11C]raclopride binding in the left dorsal caudate nucleus compared with rTMS of the left occipital cortex. There were no changes in binding in the putamen, nucleus accumbens, or right caudate. It shows that rTMS of the prefrontal cortex induces the release of endogenous dopamine in the ipsilateral caudate nucleus. The second potential mechanism has not been fully supported by experimental data and is thus hypothetical. We believe that it involves a physical inhibitory process resulting from an increased cortical output of high frequency to override spontaneous low-frequency oscillation in subcortical structures involved in EPS. Studies have shown that the abnormal oscillations in the low-frequency range (5-8 Hz) in neurons of the globus palladus and subthalamic nucleus may contribute to Parkinsonian tremor.[31] A higher frequency inputs from the cortex facilitated by αTMS may be able to inhibit the subcortical spontaneous oscillations through frequency overriding just as that occurring in the heart beats where the spontaneous oscillations from atrium, ventricle, and Purkinje's fibers are overridden by the higher frequency sinus outputs. Obviously, more direct evidence will be required to test the merits of this hypothesis.

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