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Therapeutic Effects of Individualized Alpha Frequency Transcranial Magnetic Stimulation (αTMS) on the Negative Symptoms of Schizophrenia

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Previous research in clinical electroencephalography (EEG) has demonstrated that reduction of alpha frequency (8–13 Hz) EEG activity may have particular relevance to the negative symptoms of schizophrenia. Repetitive Transcranial Magnetic Stimulation (rTMS) was utilized to investigate this relationship by assessing the therapeutic effects of stimulation set individually at each subject's peak alpha frequency (αTMS). Twenty-seven subjects, with predominantly negative symptom schizophrenia, received 2 weeks of daily treatment with either αTMS, 3 Hz, 20 Hz, or sham stimulation bilaterally over the dorsolateral prefrontal cortex. Individualized αTMS demonstrated a significantly larger ($F_{3,33} = 4.7$, $p = .007$) therapeutic effect (29.6% reduction in negative symptoms) than the other 3 conditions (< 9%). Furthermore, these clinical improvements were found to be highly correlated ($r = 0.86$, $p = .001$) with increases (34%) in frontal alpha amplitude following αTMS. These results affirm that the resonant features of alpha frequency EEG play an important role in the pathophysiology of schizophrenia and merit further investigation as a particularly efficacious frequency for rTMS treatments.

Key words: alpha rhythm/αTMS/schizophrenia/EEG/transcranial magnetic stimulation

Introduction

As introduced by Anthony Barker in 1985, transcranial magnetic stimulation (TMS) offers a noninvasive method of inducing electrical activation of the brain. In accordance with the principles of electromagnetic induction, a high voltage pulse of electricity passed through a coil placed adjacent to the scalp can generate a brief magnetic field perpendicular to the electric current flow. The magnetic field, in turn, will pass through the skull unimpeded and induce a secondary electric current in the brain.[1] The secondary current has exactly the same alternating rate with opposite direction as the original pulses in the coil. These features of electromagnetic stimulation have provided us with a unique tool to perturb or tune electric oscillatory activities in the brain.

Primarily utilized as a probe for cortical mapping of distributed neural circuits and associated cognitive, motor, or behavioral functions, TMS has proven to be an invaluable addition to the tools of functional brain research.[2] Of particular relevance to the current investigation, however, are the recent attempts to explore the therapeutic potential of the method as a unique treatment modality for a variety of neuropsychiatric disorders.[3] Repetitive TMS (rTMS), which refers to the use of grouped pulses of stimulation employed at precise frequencies to achieve a constant train of activation over brief periods of a treatment session, has become the most widely explored method of administration.

Within established rTMS treatment parameters, however, there still remains considerable uncertainty as to how best to optimize therapeutic efficacy for the various illnesses under investigation. Among such stimulation parameters that require optimization are

1. Frequency—Higher frequencies (> 10 Hz) have been commonly believed to increase cortical excitability, while lower frequencies are thought to act as inhibitory;
2. Intensity—Generally quantified for each individual as a percentage of the threshold at which motor activity can be elicited (~1–2 Tesla);
3. Duration—To reduce risk of seizure or muscle tension pain, pulse trains are normally brief (1–2 seconds), and intertrain intervals are generally 30–60 seconds; and
4. Site of Stimulation—Varies depending on patient population or specific brain functions under investigation. Central to the current study was the question of what would be the optimal stimulation frequency to use in the treatment of the negative symptoms of schizophrenia.

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While rTMS has been extensively studied in the treatment of depression and other disorders, there has been only a limited number of reports on its clinical effects in the treatment of schizophrenia.[4] Using low frequency (1 Hz) stimulation over left temporoparietal cortex, Hoffman et al.[5] reported statistically significant decreases in auditory hallucinations in schizophrenia as compared with sham stimulation. These results have also been replicated by d'Alfonso et al.[6] using similar treatment parameters. Geller et al.[7] found beneficial effects of slow (1 Hz) rTMS at suprathreshold intensity through a nonfocal stimulationed over vertex, which affected both hemispheres in 10 subjects with schizophrenia. In contrast to the low frequency approach, Rollnik et al.[8] used a fast rate rTMS of 20 Hz at 80% motor threshold (MT) in a small group of patients with schizophrenia and found that 2 weeks of daily treatment over left dorsolateral prefrontal cortex (DLPFC) significantly reduced the psychotic symptoms, as indicated by the reduction of Brief Psychiatric Rating Scale (BPRS) scores, whereas depressive and anxiety symptoms did not change significantly. With similar stimulation frequency and intensity (20 Hz and 80% MT), Cohen et al.[9] reported their findings in schizophrenia with predominant deficit syndromes, demonstrating that bilateral fast rTMS of prefrontal area might be beneficial to patients by reducing their negative symptoms.

While various parameters and their combination need to be more fully investigated, the present study was designed to compare the efficacy of different frequencies of rTMS in treating schizophrenic subjects with predominant negative symptoms, a complex syndrome that includes social withdrawal, affective flattening, poor motivation, and apathy. Compared with low (3 Hz) and high (20 Hz) frequencies, we hypothesized that frontal lobe rTMS with individualized stimulus rate at subjects' peak alpha EEG frequency (8–13 Hz) would be most effective as a treatment. This hypothesis is based on a well-documented EEG finding that patients with schizophrenia have reduced alpha activity (power and coherence) at rest[10] or during sensory and cognitive stimulations.[11,12] Studies have also shown that the decrease in alpha power was associated with patients' psychotic symptoms[13,14] and that the clinical improvement in negative symptoms following clozapine treatment was correlated with the degree of photically driven alpha EEG normalization in the frontal cortex.[15,16] Considering the resonant features of alpha EEG oscillation,[17,18] the reported intra-individual stability of alpha peak frequencies,[19,20] and the purported association of reduced alpha activity to schizophrenia symptomatology, we predicted that the stimulus rate of rTMS set individually at each subject's intrinsic peak alpha frequency would increase frontal alpha activity and, consequently, reduce the clinical symptoms.

Methods

Subjects

Twenty-seven patients diagnosed with schizophrenia (age: 37.7 ± 9.0 years old; sex: 18 males, 9 females) presenting predominantly negative symptoms and stabilized on current antipsychotic medications for at least 30 days were enrolled in the study at the outpatient clinic of the University of California, Irvine, Neuropsychiatric Center. Each patient received a structured interview with 2 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). During the subject recruitment, a minimum score of 20 on the PANSS negative symptom subscale and a maximum score of 19 on the positive symptoms subscale were 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 or indication of seizure proneness on EEG screening, major head trauma, progressive neurological diseases, high dose (> 400 mg) clozapine in the past 3 months, electric convulsion 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, institutional review board–approved, written consent before participation in any study procedures.

Procedure

Four rTMS treatments with 3 different frequencies and a sham stimulus were included in a double-blind crossover design. Each patient had an equal chance to be assigned into 2 study groups, each of which included 2 treatments (ie, alpha/sham or 3 Hz/20 Hz). Patients were kept blind to the treatment condition for the duration of the study. Treatment order of the combinations was random. Each treatment consisted of 10 daily sessions during a 2-week period, with 2 weeks of no treatment between conditions. Patients' current antipsychotic treatments were kept unchanged during the rTMS study. In each daily treatment session, a CADWELL 9-cm circular coil was placed on the middle of the forehead with the side edges reaching the areas of F_3 and F_4 EEG electrode locations. Stimulation was given 2 seconds per minute for 20 consecutive minutes per session at an intensity of 80% motor threshold, a minimal magnetic pulse that reliably induced visible contra lateral thumb movement (average intensity: 149.5 joules per pulse). The frequencies for the active stimuli were 3 Hz, individualized alpha (8–13 Hz) and 20 Hz. Rate for the alpha frequency stimulation was determined at the nearest integer of each patient's average alpha peak frequency, obtained from 5 frontal EEG leads (F_7, F_3, F_z, F_4, F_8). Sham stimulation was given by applying an unplugged coil to the forehead and an activated coil left 2 feet away behind the patient.

During the EEG recording, patients were in a supine position and asked to relax 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. Electro-oculograms (EOGs) from the outer canthus of both eyes were recorded simultaneously to monitor eye movements. The impedance of each electrode was lower than 5 KΩ. Two minutes of EEG epochs were collected and digitized by a 16-bit A/D (analog/digital) converter at the rate of 256 Hz and further processed digitally by Neurodata Inc (QND 10.2) data acquisition system. Sixty seconds of artifact free epochs were utilized for fast Fourier transformations (FFT). FFT window was set at 512 data points with 80% overlap.

Severity of psychosis, depression, and movement disorders 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 prior to first treatment), immediately following the fifth and tenth treatments, and after 2 weeks of washout for each condition. While the technician administering the rTMS procedures (SH) could not be blinded, the evaluating physicians (AG, TT, and DC), EEG technicians (YJ and AK), and patients remained unaware of the type of treatment throughout the duration of the study. A priori categorical definition for clinical response was $> 30\%$ baseline-to-posttreatment reduction, or < 16 at the end of second phase treatment when baseline score was lower than 20 on PANSS negative symptom subscale.

Statistical Analyses

Clinical data were analyzed on an intent-to-treat basis with the last observation carried forward. Patients with a baseline and at least 1 additional set of completed assessments (at least 5 treatment sessions) were included in the analysis of mean treatment effect. Efficacy in clinical ratings was evaluated by using analyses of variance (ANOVA). The models included 1 between-subjects factor of treatment, and 2 within-subjects factors of time and treatment order. Covariance for the baseline was used when significant group difference was found at the baseline. The Kruskal-Wallis test was used for post hoc comparisons of clinical responsive among treatment groups.

Raw EEG data were edited offline by an experienced technician who was blind to the treatment conditions to eliminate any significant ($> 3°$ arc) eye movements or any other type of apparent artifact. Twenty-four to thirty artifact-free epochs (512 data points per epoch) in each recording channel were calculated by a fast Fourier transform (FFT) routine to produce a power spectrum with ½ Hz frequency resolution, through which 5 consecutive EEG bands (δ: 0.5–4.0 Hz, θ: 4.5–7.5 Hz, α: 8.0–13.0 Hz, and β: 13:5–30.0 Hz) were yielded. Peak frequency and power density of each band were automatically calculated. In this study only the alpha band was reported. Variable for each channel was normalized by dividing power in every frequency band by the total energy across the entire spectrum and presented as relative power density. To further reduce the data, FFT coefficients from 19 EEG channels were clustered into 3 regional measures on both hemispheres, namely, the frontal, temporal, and parieto-occipital areas. Multivariate analysis of variance (MANOVA) with repeated measures was used to determine the main effect interactions. This model included 1 grouping factor (treatment) and 3 within-factors (time, brain region, and hemisphere). Huyhn-Feldt adjustments for degree of freedom were applied when the assumption of variance-covariance matrix to be circular in form was violated. Pearson correlation coefficients were used to test the association between changes in EEG and negative symptoms.

Results

Twenty patients finished at least 1 phase of treatment, resulting in 11 cases in the αTMS group, 8 in the sham group, 9 in the 3 Hz group, and 9 in the 20 Hz group. Before the completion of phase 1, 3 patients dropped out from the high-frequency group, 2 from the low-frequency group, 1 from the alpha frequency group, and 1 from the sham group because of the discomfort of the stimulation or the exacerbation of psychotic symptoms during the treatment. No adverse effects were found to be directly related to the rTMS in any treatment group. Two major positive results are summarized as follows:

1. Patients' negative symptoms were greatly reduced with αTMS (Figure 1). Compared with sham (8% +/− 0.2) and both low- (9% +/− 0.12) and high-frequency (−4% +/− 0.18) rTMS groups, individualized αTMS (mean stimulus rate: 8.6 Hz +/− 0.8) produced significantly greater reduction (29.6% +/− 0.27) of PANSS negative symptom scores ($F_{3,33} = 4.7$, $p = .007$). There was no significant main effect interaction among factors of treatment order, evaluation time, and group. Using $> 30\%$ improvement or < 16 endpoint rating on PANSS negative symptoms criteria, we further observed that 6 of 11 patients responded to the alpha treatment, while only 1 responded to the low-frequency, 1 to sham, and none to the high-frequency stimulation. A Kruskal-Wallis test showed the group asymmetry among the 4 treatments to be highly significant ($\chi^2 = 9.33$, $p = .009$). There was no statistical significance among the groups in positive symptom changes. Treatment effects on depressive symptoms (MADRS) and movement scales (BARS, SAS) were also not statistically significant.

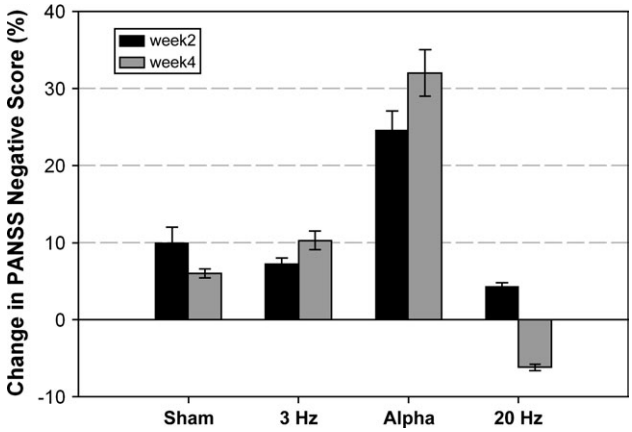

Fig. 1. Clinical response to rTMS at 3 Hz ($n = 9$), 20 Hz ($n = 9$), alpha frequency ($n = 11$), and sham ($n = 8$) immediately following 2 weeks of treatment (Week 2) and after an additional 2 weeks following end of treatment (Week 4). The level of response is shown as percent decrease (improvement) from baseline Positive and Negative Syndrome Scale (PANSS) negative symptom subscale scores.

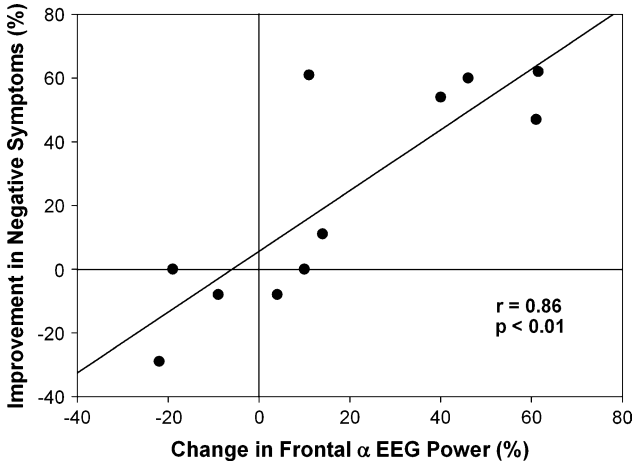

Fig. 2. Percent improvements in the Positive and Negative Syndrome Scale (PANSS) negative symptom subscale were significantly correlated with changes in the alpha band (α: 8–13 Hz) EEG in the frontal cortex of those patients receiving the individualized αTMS. Such correlations were not found for any of the other treatment groups or cortical regions examined.

2. EEG change following αTMS predicted clinical improvement (Figure 2). The individualized αTMS produced a marked increase (34% +/− 0.3) in power of the alpha EEG activity, primarily in the frontal area, while there were no significant EEG changes in sham (0 +/− 0.19), low-frequency (14% +/− 0.31), or high-frequency treatment groups (6% +/− 0.32). Analysis of variance with repeated measure (MANOVA) revealed a significant difference among the treatment groups ($F_{2,126} = 3.27$, $p = .03$). Correlational analyses demonstrated that improvements in negative symptoms following αTMS treatment were highly associated with the degree of alpha EEG power increment in the frontal lobe ($r = 0.86$, $p = .001$) but not in the central, temporal, or parieto-occipital areas. These data suggest that the more alpha power increased in the frontal lobe following αTMS, the greater the improvement in negative symptoms.

Discussion

While the parameter choice of rTMS treatment for psychosis remains controversial, our study using individualized alpha frequency and motor threshold–based intensity demonstrated a significant therapeutic effect on the negative symptoms of schizophrenia. These improvements were highly correlated with the degree of patients' alpha EEG enhancement in the frontal areas. These findings are consistent with our previous studies showing that the effects of antipsychotic treatment with clozapine on negative symptoms were predicted by the degree of alpha EEG normalization.[15,16]

Findings of the present study also support an important notion that EEG of alpha band has strong resonant features that can be tuned or perturbed with proper stimulation.[17,18,21] In addition to sensory stimulations,[21,22] direct electromagnetic manipulations of brain activity also appear to be an effective method of evoking resonant responses, as long as the stimulation rates are close enough to the intrinsic frequency of the alpha rhythm. We find these results to be particularly interesting given that an increasing number of studies have shown that high-order cognitive functions may be carried out by coherent neural processing across multiple regions in the brain,[23,24] where alpha EEG may provide a gating mechanism for the synchrony among different areas.[25] It has been demonstrated, for example, that when a cat has been stimulated with a sensory stimulation, an increased coherence in the alpha range between all structures in the visual pathway, hippocampus, and reticular formation could be observed.[26] Furthermore, Klimesch, Schimke, and Pfurtscheller[27] and others[28] have provided clear evidence of a positive, consistent relationship between working memory performance and mean alpha activity.

On the other hand, patients with schizophrenia often have some degree of power or coherence reduction in alpha-band EEG activity,[10] particularly during perceptual or cognitive activation.[11,12] Using a visual stimulation paradigm with repetitive light flashing, we have demonstrated that alpha EEG photic driving is a reliable and specific index in studies of mental disorders.[20] Compared to normal subjects, drug-free schizophrenic individuals have significantly reduced power density in the alpha EEG photic responses.[19,20] Furthermore, we have found that the reduced EEG photic driving in schizophrenics could be normalized by effective treatment with clozapine. The increment of the EEG photic driving produced by clozapine was positively correlated with

patients' clinical improvement in negative symptoms, assessed by BPRS. Patients who clinically responded to the treatment had significantly greater increase in photic driving than those who did not respond.[15,16] Consistent with these discoveries, the present study demonstrated for the first time that direct manipulation with αTMS could alter the alpha EEG based on the physics of resonance and improve negative symptoms in schizophrenia. It suggests strongly that alpha EEG and negative symptoms may have a causal relationship and, therefore, further investigations are needed.

Some limitations of the current study should also be discussed before any conclusions can be drawn. Crossover design has its economic benefit when the sample size is small. The drawback, however, is the potential confound of carryover effects, which may significantly alter the results. In the present study a 2-week break between different stimulations might not have been enough to completely wash out the carryover effects. Also, to solve the common problem of residual magnetic field in sham stimulus when a tilted coil is applied, we used an unplugged coil. Although the acoustic effect was presented by another active coil in close proximity, the somatic sensation of scalp muscle contractions was missing. A third limitation was the uncontrolled ongoing medication. Although patients in this study all met the predefined clinical criteria of stability on their current dose, the possibility of an rTMS-drug interaction could not be entirely excluded. Furthermore, a more rigorous assessment of the merits of utilizing individualized αTMS must also include a condition with the stimulus rate fixed at a frequency within the alpha band (8–13 Hz) to determine whether the selection of individualized alpha would have a superior effect to fixed frequencies in this range, as hypothesized.

Conclusion

Drawing on previous findings linking a reduction in the power density and coherence of alpha frequency EEG with the negative symptoms of schizophrenia, this study hypothesized that the use of individualized alpha frequency rTMS would provide a superior treatment effect than other stimulation frequencies. It was proposed that the resonant "tuning" of the peak alpha oscillations would serve to increase the power density in this frequency range and thereby improve the negative symptoms. The results have provided support for these hypotheses and are interpreted as further evidence to the critical relationship of alpha-rhythm oscillations to the pathophysiology of schizophrenia. Furthermore, these findings suggest that the use of alpha frequency as a stimulation parameter for rTMS merits further controlled trials to more thoroughly investigate its potential efficacy as a treatment for the negative symptoms of schizophrenia.

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