Published in final edited form as:
J Neuropsychiatry Clin Neurosci. 2010 ; 22(1): 75–84. doi:10.1176/appi.neuropsych.22.1.75.

Subgenual Cingulate Theta Activity Predicts Treatment Response of Repetitive Transcranial Magnetic Stimulation in Participants With Vascular Depression

Kenji Narushima[1,2], **Laurie McCormick**[2], **Throu Yamada**[3], **Robert Thatcher**[4], and **Robert G. Robinson**[2]

[1]The Section of Psychiatry and Behavioral Sciences at Tokyo Medical and Dental University Graduate School in Bunkyo-ku, Tokyo, Japan

[2]University of Iowa, Carver College of Medicine; Dept of Psychiatry, 200 Hawkins Drive, Iowa City, IA 52242

[3]University of Iowa, Carver College of Medicine; Dept of Neurology, 200 Hawkins Drive, Iowa City, IA 52242

[4]The Department of EEG and NeuroImaging Laboratory at Bay Pines VA Medical Center in St. Petersburg, Florida

Abstract

Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for depression. Increased metabolism in the anterior cingulate cortex (ACC) is a known predictor for antidepressant response. The authors assessed whether increased theta power within the ACC predicts rTMS response in participants with vascular depression. Sixty-five participants were randomized to active or sham rTMS. Outcome was assessed using the Hamilton Depression Rating Scale. Electroencephalography was obtained, and comparisons were made among each group with a normative database using low-resolution electromagnetic tomography. Results suggest that vascular depression participants respond well to rTMS and that increased low-theta power in the subgenual ACC predicts response to rTMS.

A modern apparatus of repetitive transcranial magnetic stimulation (rTMS) was developed in Great Britain in 1985.[1] Since then, rTMS has been utilized to provide noninvasive brain stimulation for research and treatment purposes. The most frequent application of rTMS in psychiatry has been as a treatment for major depression, and the first controlled treatment study was published in 1996.[2] Although a large number of studies have suggested that rTMS is efficacious against depression, a recent review found that the efficacy can be quite variable.[3] This may be due to the fact that the etiological factors underlying major depression are heterogeneous, causing some forms of depression to respond better to rTMS than others. Repetitive transcranial magnetic stimulation has already been approved as a standard treatment procedure for depression in some countries such as Canada and Israel; however, it has only recently been approved by the Food and Drug Administration in the United States.

The term “vascular depression” has been used to describe depression in elderly patients with cerebrovascular disease. A causal relationship between cerebrovascular disease and late-life depression is supported by evidence such as coexistence of depression with hypertension, coronary artery disease, and multiple hyperintensities on brain imaging.[4] Patients with late-life depression often have a chronic, treatment resistant course and frequently meet criteria for vascular depression.[5]

Predictors of response to different antidepressant treatment modalities are a growing area of clinical research interest. Higher than normal activity in the rostral anterior cingulate cortex (ACC) has been shown to predict response to antidepressant medication in patients with major depression.[6–9] High theta power in the rostral ACC has also been found to predict response in a similar population.[10] This same group found that metabolism and theta activity are linked in this region.[11] However, functional abnormalities in this region do not change in response to antidepressant treatment. Treatment response to antidepressants has been correlated to change in the subgenual region of the ACC.[12] It is unclear whether this is a normalization of high metabolism or a resetting to a new lower level of metabolism in this region.[13] The subgenual ACC has become a target for deep brain stimulation, which has already shown efficacy in treatment-resistant depression.[13] In the present study, we hypothesized that abnormal theta activity occurs within the rostral and/or subgenual regions of the ACC in patients with vascular depression and may predict an antidepressant response to rTMS.

Materials and Methods

Participants

Sixty-five participants with medication resistant vascular depression underwent EEG recordings before and after a course of rTMS. They had been recruited from both outpatient and inpatient clinics of the Department of Psychiatry at the University of Iowa Hospitals and Clinics and the Iowa City Veterans Affairs Medical Center, as well as through advertisements in metropolitan areas in the state of Iowa, between May 2002 and October 2006.

The inclusion criteria for this study were age between 50 and 90 years old; major depressive disorder (as diagnosed by the DSM-IV-TR using the Present State Examination[14] modified to identify DSM-IV-TR) with onset after age 50 and a score above 14 on the 17-item Hamilton Depression Rating Scale (HAM-D); a history of stroke or at least three of the following cardiovascular risk factors: (a) arterial hypertension, (b) diabetes mellitus, (c) obesity, (d) hyperlipidemia, or (e) smoking; and unresponsiveness to at least one antidepressant given at an adequate dose and length with no compliance issues (as assessed by the “Antidepressant Treatment History Form”).[15] Exclusionary criteria included left frontal cortex lesion or hemorrhagic stroke to avoid rTMS induced seizure; life-threatening physical illness; neurodegenerative disorder; clinical dementia (Clinical Dementia Rating Scale score >0.5)[16]; severe aphasia (i.e., inability to complete part 1 of the Token Test)[17]; suicidal thought, plan, or delusion; substance abuse within the prior 2 years; prior seizure or traumatic brain injury; and any metallic device which would preclude an MRI scan. If the participants were taking antidepressants, these were discontinued for at least 2 weeks before rTMS (except for fluoxetine where a minimum discontinuation of 3 weeks was required). Written informed consent was obtained from all participants. This project was conducted as approved by the Institutional Review Board at the University of Iowa Hospitals and Clinics and Iowa City Veterans Affairs Medical Center.

Initially, a total of 502 participants were screened; of these, 97 met our inclusion criteria and agreed to enroll in this study (Figure 1). Among these 97 participants, five withdrew before treatment. Among the remaining 92 participants, 65 who had rTMS after July 2003 were given an EEG evaluation. Among these, 43 participants were randomly assigned to active rTMS; 12 received a total of 12,000 stimulations whereas 31 had 18,000 stimulations. Those two groups were combined into a single group for data reduction, because there were no significant differences in their demographic background, clinical presentation, or primary outcomes in post hoc analyses. Among these remaining 43 participants, two refused an initial EEG examination and six participants did not return for their follow-up evaluation;

thus, a total of eight participants were withdrawn from the active treatment group. Of the remaining 35 participants, three were excluded due to poor quality recording. Thus, the final number in the active treatment group was 32. Among 22 participants assigned to sham stimulation, two refused an initial EEG recording and seven participants did not have a follow-up evaluation due to scheduling difficulties. Among the remaining 13 participants, two had a poor quality EEG. Thus, the final number in the sham treatment group was 11 (Figure 1). All participants successfully completed the full 2-week course of rTMS with no significant adverse effects. There were no significant differences in demographic background between participants who completed the study and those who were withdrawn.

Lesion Location

Magnetic resonance imaging (MRI) scans were obtained for all participants except two due to scheduling problems. Scans were evaluated for anatomical location and volume of the hyperintensities by radiologists who were blind to the clinical findings and further processed using locally developed BRAINS2 software (www.psychiatry.uiowa.edu/mhcrc/IPLpages/BRAINS.htm). The validity of this methodology has been demonstrated in previous publications.[18]

Neuropsychiatric Evaluations

The 17-item HAM-D[19] was employed before and within 1 week after a 2-week course of rTMS. HAM-D constitutes a valid measurement of depressive symptoms among participants with vascular depression.[20] A decrease of at least 50% in HAM-D scores was defined as “response” to rTMS. “Remission” was defined by a decrease of at least 50% on HAM-D and a final HAM-D score below 9. The HAM-D was given by trained research assistants who were blind to the clinical/treatment information. The participants were also given a Mini-Mental State Examination[21] at the same visit. A full description of the neuropsychiatric evaluations has been published elsewhere.[22]

rTMS Procedure

Localization of the Stimulation Site—rTMS procedure was described in detail in our prior publication. Briefly, it involved localization of the stimulation site in the left dorsolateral prefrontal cortex using Brainsight Frameless (www.magstim.com/brainsight/). A landmark was picked up on the cortex corresponding to the midpoint of the middle frontal gyrus. Finally, the Talairach coordinates of the landmark in both the anterior-posterior and dorsal-ventral directions were checked. This landmark, and thus the stimulation site, lay within the conservative range of Talairach coordinates for Brodmann’s area 46 as described elsewhere.[23]

Stimulation Parameters and Monitoring—rTMS was performed using a Magstim Super Rapid Stimulator (Jali Medical, Inc.) with 70 mm figure-8 coils. The participants were randomly assigned to three groups; two groups received active rTMS over the left dorsolateral prefrontal cortex at a frequency of 10 Hz and an intensity of 110% of the motor threshold during 6 seconds (the motor threshold was determined as the lowest stimulator intensity that induced a motor evoked potential of at least 50 mV in at least five of 10 trials using the first dorsal interosseous muscle). A total of 20 trials were given (separated by 1 minute pauses) per session. Treatment was administered over 10 days for a total cumulative dose of 12,000 pulses (n=12) or 18,000 pulses (n=31). Sham stimulation was performed using a sham coil, which was identical to the stimulating coil with vibration and noise (albeit without actual cortical stimulation).

EEG Recording

The EEG recordings were obtained before and within 1 week after a series of rTMS. EEG was recorded for at least 20 minutes using an electrode cap with ten electrodes from 19 scalp locations based on the international 10/20 system (FP1/2, F3/4, C3/4, P3/4, O1/2, F7/8, T3/4, T5/6, Fz, Cz, Pz), using linked ears as a reference. Electrode impedances were under 5Ω. Data were collected digitally with a sampling rate of 200 Hz, and a digital band-pass filter (1–70 Hz) was used offline.

For all participants, EEG acquisition occurred with a Neurofax system (Nihon Kohden). At least 3 minute segments of EEG were recorded during an eyes-closed resting condition. Each EEG recording was examined to remove artifacts by using NeuroGuide software (http://www.appliedneuroscience.com), which was further visually confirmed by neuroscientists who were blind to the clinical information (KN, TY). Nonoverlapping, artifact-free 60 sec epochs were selected from each recording. Split-half and test-retest reliability tests were conducted and only records with >95% split-half reliability and >90% test-retest reliability were entered into the following analyses.

LORETA Computation

All EEG epochs were further analyzed with low resolution electromagnetic tomography (LORETA-KEY software package; www.uzh.ch/keyinst/loreta), which interfaces with NeuroGuide. From the scalp-recorded electrical potential, LORETA computed the three-dimensional space electrical potential distribution. LORETA utilizes a whole-brain approach, and computations were restricted to cortical gray matter. The spatial resolution was 7 mm, and the solution space contained 2,394 voxels with spectral resolution of 1 Hz.

Analyses were conducted in a stepwise fashion. All available EEG epochs were subjected to a whole brain cross-spectrum analysis for the following EEG bands: delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz). We further divided the theta band into low (4–5 Hz) and high (6–7 Hz) frequencies based on the fact that Pizzagalli et al.[10] found that high theta activity (6.5–8 Hz) predicted a response to antidepressant medication. LORETA computed current density as the linear, weighted sum of the scalp electrical potentials and squared this value to yield power of current density for individual frequencies in each voxel. The LORETA solution was normalized to a total power of 1 and log-transformed for each band.

Region-of-interest clusters were analyzed for the regions corresponding to the rostral and subgenual ACC as provided by the LORETA legend, which allows identification of the average power for each frequency of every voxel to be analyzed separately. There are 188 voxels for the entire ACC. The subgenual region that corresponded to the entire BA25 was made up of 29 voxels (total volume 9.95 cm^3), while the rostral region was made up of 52 voxels (17.84 cm^3). Compared to a normative database, LORETA units in these ACC subregions at baseline were analyzed by cluster t statistics. For comparison to the nondepressed, normal control population, an age-adjusted normative module within NeuroGuide was employed which was based on 625 individuals from 2 months to 82 years of age who met specific clinical standards including no history of neurological disorders or behavioral disorders as well as attainment of an age-appropriate level of education.[24] LORETA is quite accurate when there are no artifacts in the data as evidenced from over 500 peer reviewed articles, which have found that LORETA compares favorably to the more classical functional imaging methods, such as PET and fMRI.25 In order to solve the ill-posed inverse problem (i.e., how to determine electric sources based on scalp recorded surface data), LORETA makes a “smoothness assumption” that neighboring voxels should have maximally similar activity. The LORETA algorithm allows for correct localization at a

special resolution to within 1 voxel or 7 mm resolution on average.[26] Several studies provided validation for EEG-based LORETA analysis using MRI,[27] fMRI,[28] or PET.[10]

Hyperintensity Lesions

Among the 41 participants who completed a brain MRI scan, five scans were not analyzed due to bad segmentation or poor imaging quality. Among the remaining 36 participants, 27 showed multiple hyperintensities. There were no significant differences between the responders and the nonresponders in the locations or total volume of hyperintensity lesions. Full descriptions of the imaging analyses have been published previously.[22] Only 8% of patients previously had clinical stroke (no significant difference among the treatment groups).

Other Statistical Analyses

Between-group comparisons were carried out using means, standard errors, and analysis of variance (ANOVA). Frequency distributions were compared using chi-square tests or, where appropriate, Fisher's exact test. All tests were two-tailed; p value was set at 0.05

Results

Patient Characteristics

This study was based on a total of 43 participants, 32 in the active treatment group and 11 in the sham group. There were no significant differences between these two groups in their background. When the active treatment group was divided into responders and nonresponders as shown in Table 1, years of education were significantly different ($F=3.65$, $df=2, 38$, $p=0.04$). This difference had no statistically significant effect on any of our findings.

Efficacy of rTMS for Vascular Depression

Before rTMS treatment, HAM-D scores were not significantly different between the active and the sham groups. Among the active group, 14 out of 32 participants responded to the rTMS (43.8%) and only one responded to the sham stimulation (9.1%). There was a significant difference between the active and the sham groups in the response rate ($\chi^2=5.06$, $df=42$, $p=0.02$). The remission rate was 34.4% (n=11) in the active group and 0% in the sham group. The remission rate was also significantly different between these two groups (Fisher's exact test, $\kappa=0.21$, $p=0.04$).

Electrophysiological Activity in the ACC Before and After rTMS

The initial whole brain analysis, which analyzed participants who later responded to rTMS (n=14) relative to healthy comparison subjects, showed significantly greater than normal low-theta power only in the posterior most portion of the subgenual ACC prior to rTMS treatment ($t=2.28$, $df=13$, $p<0.05$; Figure 2, panel A). The nonresponders (n=18) did not show the same higher than normal electrophysiological activities in this area (Figure 2, panel B). A region-of-interest analysis of the subgenual ACC cluster also confirmed that there was a significant difference in baseline (i.e., before rTMS) low-theta power between those who went on to respond versus those who did not respond to active rTMS ($F=4.18$, $df=1, 30$, $p=0.04$; Figure 3). There was no difference in the rostral ACC region between the responders and the nonresponders ($F=0.005$, $df=1, 30$, $p=0.94$) at the same evaluation. After rTMS, the active responder group showed normalization of higher than normal low-theta power in the subgenual ACC (i.e., no significant difference in low-theta power compared to the normative database). A posttreatment comparison between the responders and the nonresponders to active rTMS showed that there was also no longer any significant

difference in low-theta activity in the subgenual (F=0.02, df=1, 30, p=0.90) or the rostral ACC (F=0.07, df=1, 30, p=0.80).

The low-theta power in the subgenual ACC was correlated to total HAM-D scores among all the participants prior to rTMS (Spearman ρ=0.38, p=0.01). The positive and significant correlation was also found between percent changes in low-theta power in this region and total HAM-D score among participants with active rTMS (Spearman ρ=0.45, p<0.01; Figure 4).

Discussion

The present study showed that nearly half of the drug-resistant vascular depression participants responded to rTMS, whereas virtually none of the participants who received sham rTMS responded. This study also found that increased pretreatment low-theta power in the subgenual ACC was associated with the antidepressant response from rTMS. To our knowledge, this is the first study to identify a prospective predictor for antidepressant response to rTMS among participants with treatment-resistant vascular depression using EEG analyzed with LORETA.

The efficacy of rTMS for depression has been shown to be quite variable and only slightly better than the sham condition in some studies (e.g., 37% response to active treatment versus 20% to sham).3 A high response rate to sham stimulation has been one of the most significant issues affecting the consideration of efficacy of rTMS. Given the relatively high efficacy of active rTMS (43.8%) and the low response rate to sham (9.1%) in our study, vascular depression seems to be a quite appropriate population to be treated by rTMS. It is crucial, however, to further define appropriate participants who are likely to respond to rTMS. Our analyses (Figure 2, panel A) revealed that responders displayed, on average, electrophysiological brain activity in the subgenual ACC (defined as 4–5 Hz power) that was 2.28 standard deviations above the control, whereas the nonresponders (Figure 2, panel B) did not display any statistical differences. Region-of-interest analysis of the subgenual ACC showed a positive and significant correlation between percent changes in low-theta power and total HAM-D scores among the actively treated participants (Spearman ρ=0.45, p<0.01; Figure 4). In addition, before the rTMS stimulation, there was a positive and moderate correlation between low-theta power in the subgenual ACC and total HAM-D score among all the participants (Spearman ρ=0.38, p=0.01). These correlations suggest a significant role for the subgenual ACC in the development of depression among patients with vascular diseases.

Functional brain imaging has played a primary role in the search for predictors of response to different treatment modalities for major depression, and EEG with LORETA can be used in a similar way.[29] The brain region with the greatest prospect of pretreatment prediction is the rostral ACC.[6–8] Metabolic and electrophysiological activity changes in depression are linked in this particular part of the brain.[10] Although the rostral ACC is anatomically connected to the subgenual ACC, these regions are cytoarchitecturally distinct.[9, 30–32] The subgenual ACC is considered a more archaic region than the rostral ACC; has extensive connections with other parts of the brain such as the amygdala, raphe nuclei, and brain stem autonomic nuclei; and is involved in emotional processing, monoaminergic neurotransmitter release, and autonomic regulation.[33] While abnormal function has been found in both the rostral and the subgenual ACC in major depression, only the subgenual ACC has been associated with a reduction in volume,[31,34] and this may represent the core abnormality of treatment resistant depression.[35] Although elevated activity in the rostral ACC has been shown to predict response to pharmacological treatment,[9,10] response to antidepressant treatment has been shown to be primarily mediated by the subgenual ACC. A recent study

by Kitou and Koga.[36] reported that active rTMS decreases regional blood flow in the subgenual ACC and is associated with efficacy, and similar findings have been reported using antidepressant medication[12] and deep brain stimulation.[13] The subgenual ACC is also known to become activated during normal sadness[37] and may be overly active in patients with major depression. These findings suggest that higher than normal activity in this specific brain region predicts response to different treatment modalities.38 Although rTMS does not stimulate the subgenual ACC directly, the blood flow studies of Kitou and Koga.[36] show several brain regions being activated from rTMS, suggesting current spread from the dorsolateral prefrontal cortex through neighboring structures known to have significant connections to the subgenual ACC.[32] Compared to previous publications, the presentation of regional brain abnormalities was slightly different in our participants who eventually responded to the treatment, such as regions (rostral or subgenual ACC) or changes in activity (increase or decrease), which may be attributable to the subtype of depression and ability to respond to different forms of antidepressant therapy.

Limitations of this study include the fact that the majority of participants were Caucasian and from a relatively higher socioeconomic status that may not be representative of the depressed population as a whole. Second, attrition rates were high, and we were unable to obtain an equal amount of evaluations in the sham group due to study design. Third, LORETA has been utilized by multiple experienced groups in this field of research over the past 10+ years; however, the use of a standardized normative database is a relatively new modality for confirming differences with healthy comparison subjects. Similarly, there is currently no database or information about theta power in the ACC in subjects who have had similar vascular problems but without symptoms of depression. Additionally, there was no further follow-up evaluation for recurrence of depression, no qualitative evaluation for the sham stimulation, no voltage data applied, and no functional neuroimaging provided. Lastly, although vascular depression is considered a distinct diagnostic subtype, there are still no universally accepted diagnostic criteria for clinical vascular depression.

Since abnormal generation in a part of the theta band was found in vascular depression participants who responded best to rTMS, these findings suggest that normal theta activity in the subgenual ACC is an important aspect of emotion regulation, which when disrupted is linked to depression. Larger scale prospective rTMS studies that also include functional imaging to localize the path of rTMS current simulation are necessary to validate the findings in this study. Improved efficacy of rTMS, however, might be achieved among patients with vascular depression who show increased 4–5 Hz theta power in the subgenual ACC at baseline.

Acknowledgments

Presented in part at the American Psychiatric Association Annual Meeting in Washington, DC, May 5, 2008 (the 2007–2008 APA/Lilly Resident Research Award).

We thank Teresa Kopel, M.A., Stephanie Rosazza, B.S., Jose A. Abreu, J. Todd Kosier, B.S., and Michael C. Brumm, B.S., for participant recruitment and EEG collection. We are indebted to the Department of Psychiatry at the University of Iowa Hospitals and Clinics and the Department of Psychiatry at the Iowa City Veterans Affairs Medical Center in Iowa City for allowing us to access the participants for inclusion in the study. This study was supported in part by National Institute of Mental Health R01 grant MH63405 (RGR).

References

1. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985; 1:1106–1107. [PubMed: 2860322]

2. Pascual-Leone A, Rubio B, Pallardo F, et al. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet. 1996; 348:233–237. [PubMed: 8684201]
3. Brunelin J, Poulet E, Boeuve C, et al. Encephale. 2007; 33:126–134. (French). [PubMed: 17675907]
4. Alexopoulos GS, Meyers BS, Young RC, et al. "Vascular depression" hypothesis. Arch Gen Psychiatry. 1997; 54:915–922. [PubMed: 9337771]
5. Krishnan KR, Taylor WD, McQuoid DR, et al. Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. Biol Psychiatry. 2004; 55:390–397. [PubMed: 14960292]
6. Saxena S, Brody AL, Ho ML, et al. Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression. Am J Psychiatry. 2003; 160:522–532. [PubMed: 12611834]
7. Brody AL, Saxena S, Silverman DH, et al. Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine. Psychiatry Res. 1999; 91:127–139. [PubMed: 10641577]
8. Davidson RJ, Irwin W, Anderle MJ, et al. The neural substrates of affective processing in depressed patients treated with venlafaxine. Am J Psychiatry. 2003; 160:64–75. [PubMed: 12505803]
9. Mayberg HS, Brannan SK, Mahurin RK, et al. Cingulate function in depression: a potential predictor of treatment response. Neuroreport. 1997; 8:1057–1061. [PubMed: 9141092]
10. Pizzagalli D, Pascual-Marqui RD, Nitschke JB, et al. Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. Am J Psychiatry. 2001; 158:405–415. [PubMed: 11229981]
11. Pizzagalli DA, Oakes TR, Davidson RJ. Coupling of theta activity and glucose metabolism in the human rostral anterior cingulate cortex: an EEG/PET study of normal and depressed subjects. Psychophysiology. 2003; 40:939–949. [PubMed: 14986847]
12. Kennedy SH, Konarski JZ, Segal ZV, et al. Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. Am J Psychiatry. 2007; 164:778–788. [PubMed: 17475737]
13. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005; 45:651–660. [PubMed: 15748841]
14. Wing, J.; Cooper, J.; Sartorius, N. The Measurement and Classification of Psychiatric Symptoms: An Instructional Manual for the PSE and CATEGO Programs. New York: Cambridge University Press; 1974.
15. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the cumulative illness rating scale. Psychiatry Res. 1992; 41:237–248. [PubMed: 1594710]
16. Morris JC, Storandt M, Miller JP, et al. Mild cognitive impairment represents early-stage Alzheimer's disease. Arch Neurol. 2001; 58:397–405. [PubMed: 11255443]
17. De Renzi E, Faglioni P, Previdi. Increased susceptibility of aphasics to a distractor task in the recall of verbal commands. Brain Lang. 1978; 6:14–21. [PubMed: 698780]
18. Ho BC, Andreasen NC, Nopoulos P, et al. Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. Arch Gen Psychiatry. 2003; 60:585–594. [PubMed: 12796222]
19. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960; 23:56–62. [PubMed: 14399272]
20. Steffens DC, Krishnan KR. Structural neuroimaging and mood disorders: recent findings, implications for classification, and future directions. Biol Psychiatry. 1998; 43:705–712. [PubMed: 9606523]
21. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]
22. Jorge RE, Moser DJ, Acion L, et al. Treatment of vascular depression using repetitive transcranial magnetic stimulation. Arch Gen Psychiatry. 2008; 65:268–276. [PubMed: 18316673]

23. Rajkowska G, Goldman-Rakic PS. Cytoarchitectonic definition of prefrontal areas in the normal human cortex, II: variability in locations of areas 9 and 46 and relationship to the Talairach coordinate system. Cereb Cortex. 1995; 5:323–337. [PubMed: 7580125]
24. Thatcher RW, North D, Biver C. Evaluation and validity of a LORETA normative EEG database. Clin EEG Neurosci. 2005; 36:116–122. [PubMed: 15999907]
25. Pascual-Marqui RD, Esslen M, Kochi K, et al. Functional imaging with low-resolution brain electromagnetic tomography (LORETA): a review. Methods Find Exp Clin Pharmacol. 2002; 24(suppl C):91–95. [PubMed: 12575492]
26. Pascual-Marqui RD. Review of methods of solving the EEG inverse problem. International Journal of Bioelectromagnetism. 1999; 1:75–86.
27. Worrell GA, Lagerlund TD, Sharbrough FW, et al. Localization of the epileptic focus by low-resolution electromagnetic tomography in patients with a lesion demonstrated by MRI. Brain Topogr. 2000; 12:273–282. [PubMed: 10912735]
28. Seeck M, Lazeyras F, Michel CM, et al. Non-invasive epileptic focus localization using EEG-triggered functional MRI and electromagnetic tomography. Electroencephalogr Clin Neurophysiol. 1998; 106:508–512. [PubMed: 9741750]
29. Saletu B, Anderer P, Saletu-Zyhlarz GM, et al. EEG mapping and low-resolution brain electromagnetic tomography (LORETA) in diagnosis and therapy of psychiatric disorders: evidence for a key-lock principle. Clin EEG Neurosci. 2005; 36:108–115. [PubMed: 15999906]
30. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behavior. Brain. 1995; 118:279–306. [PubMed: 7895011]
31. Drevets WC, Price JL, Simpson JR Jr, et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature. 1997; 386:824–827. [PubMed: 9126739]
32. Johansen-Berg H, Gutman DA, Behrens TE, et al. Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. Cereb Cortex. 2007; 18:1374–1383. [PubMed: 17928332]
33. Drevets WC. Prefrontal cortical-amygdalar metabolism in major depression. Ann N Y Acad Sci. 1999; 877:614–637. [PubMed: 10415674]
34. Coryell W, Nopoulos P, Drevets W, et al. Subgenual prefrontal cortex volumes in major depressive disorder and schizophrenia: diagnostic specificity and prognostic implications. Am J Psychiatry. 2005; 162:1706–1712. [PubMed: 16135631]
35. Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimized treatment. Br Med Bull. 2003; 65:193–207. [PubMed: 12697626]
36. Kitou N, Koga Y. RCBF change after low rate rTMS among treatment resistant depression. Jpn J Clin Neurophysiol. 2007; 35:389.
37. Liotti M, Mayberg HS, Brannan SK, et al. Differential limbic–cortical correlates of sadness and anxiety in healthy subjects: implications for affective disorders. Biol Psychiatry. 2000; 48:30–42. [PubMed: 10913505]
38. Siegle GJ, Carter CS, Thase ME. Use of fMRI to predict recovery from unipolar depression with cognitive behavior therapy. Am J Psychiatry. 2006; 163:735–738. [PubMed: 16585452]

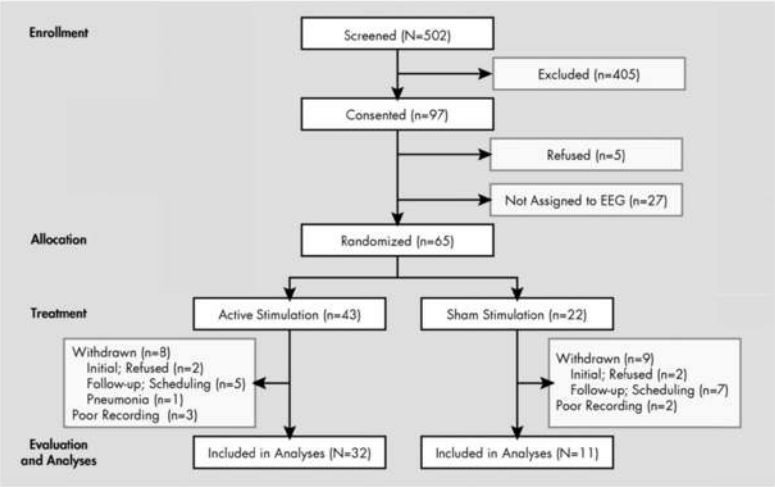

Figure 1.
Flow Chart of Inclusion of Subjects into Active Versus Sham rTMS Groups

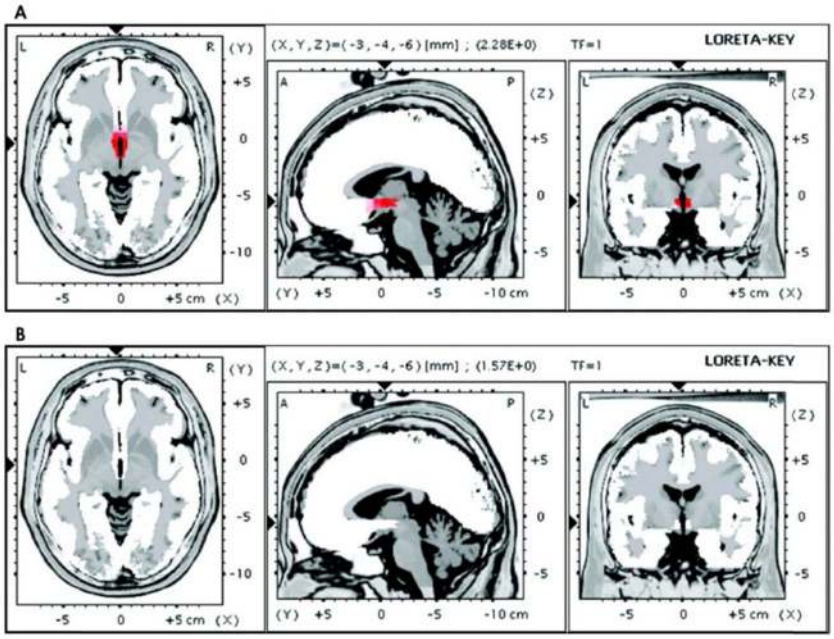

Figure 2. Z Scores of Lw-theta Pwer (4–5 Hz) in Pre-rTMS Responders versus Non-Responders with LORETA

(A) A whole brain analysis of pretreatment data for rTMS responders (n=14) normalized against a standardized age-adjusted normative database within NeuroGuide (i.e., Z scores) revealed significantly higher than normal Z scores in low-theta power (4–5 Hz) within the subgenual ACC (BA25). Only the BA25 voxels which had significantly increased low-theta power are shown in red color. (B) A similar analysis of pretreatment data for rTMS non-responders (n=18) revealed no higher or lower theta activity or statistically significant Z scores before rTMS.

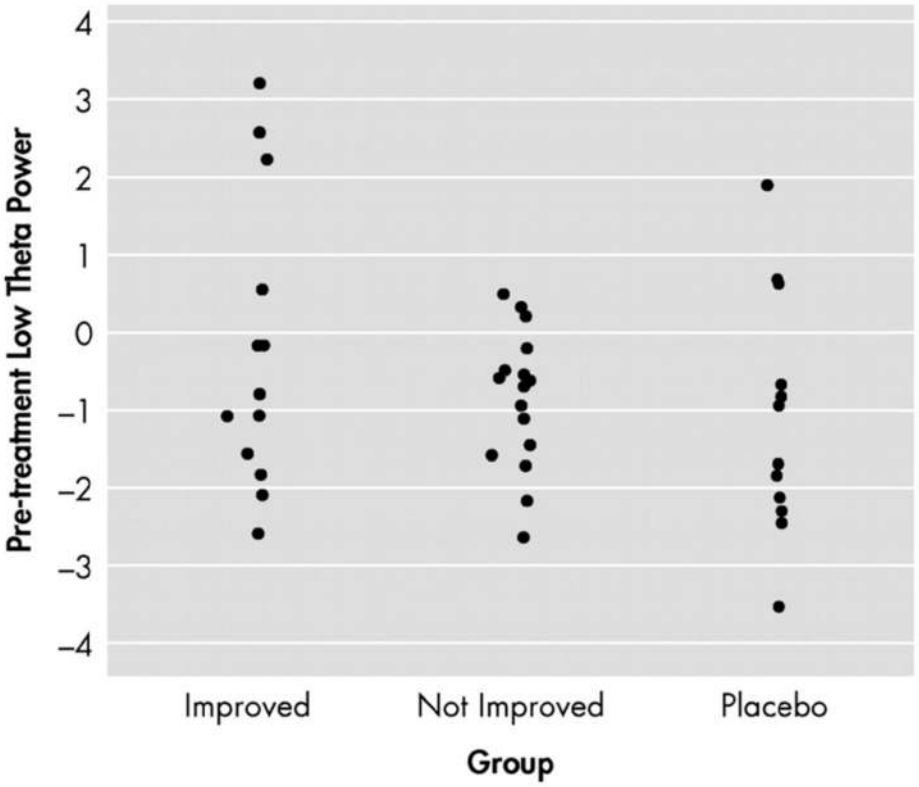

Figure 3. Pretreatment Low Theta Power in the Subgenual ACC

Scatterplot showing pretreatment low-theta power in the subgenual ACC among the three groups revealed a significant difference in low-theta power between those who responded versus those who did not respond to active rTMS prior to rTMS ($F=4.18$, $df=1, 30$, $p=0.04$; comparison between the active two groups).

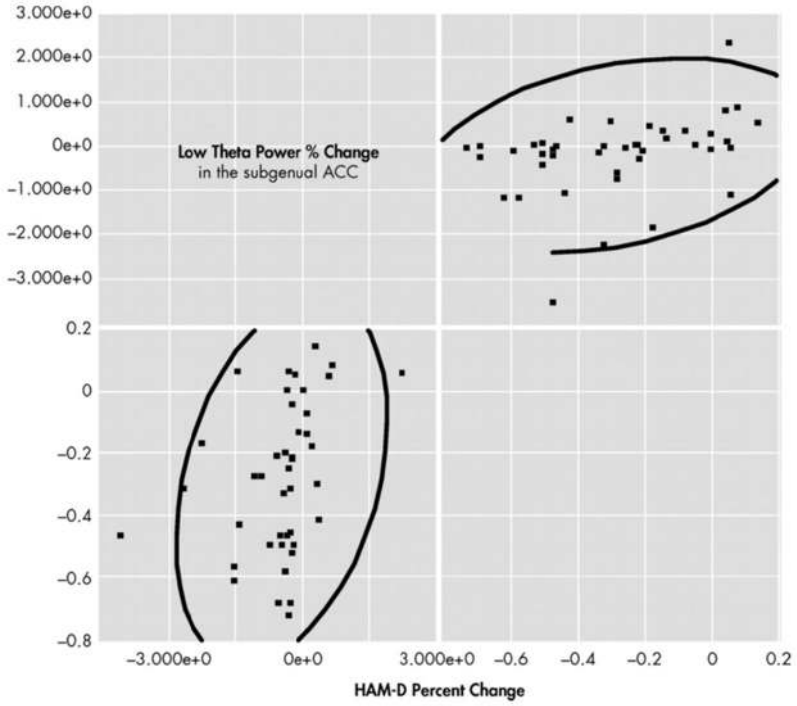

Figure 4. Correlation Between Subgenual ACC Low Theta Power Percent Change and HAM-D Percent Change

Scatterplot demonstrating that there is a significant and positiv ve correlation between % changes in low-theta power in the subgenual ACC and total HAM-D among participants with active rTMS (Spearman $\rho=0.45$, $p<0.01$).

HAM-D=Hamilton Depression Rating Scale; ACC=anterior cingulate cortex

J Neuropsychiatry Clin Neurosci. Author manuscript; available in PMC 2013 June 20.

TABLE 1

Participant Demographics for Participants Who Received Active rTMS

	Active Group (n=32)						
	Responder (n=14)		Nonresponder (n=18)		Placebo Group (n=11)		
Characteristic	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Difference**
Age (years)	60.1	2.2	65.9	2	61.5	2.5	NS
Education (years)	14.9	0.5	13.1	0.5	14.6	0.7	<0.05 *
HAM-D pre	17.7	1.1	15.6	1.3	16.8	1.9	NS
HAM-D post	8.1	0.7	13.7	1.2	13.0	1.6	<0.05
MMSE	28.1	0.5	27.8	0.4	27.5	0.5	NS
MRI hyperintensities (% of total brain volume)	0.55	0.27	0.83	0.24	0.63	0.31	NS
	n	**%**	**n**	**%**	**n**	**%**	
Male sex	5	36	8	44.4	5	45.5	NS
Caucasian race	14	100	17	94.4	11	100	NS
Married (or not living alone)	9	64.3	10	55.6	6	54.6	NS
Hollingshead class IV or V	2	14.3	4	22.4	0	0	NS

NS=not significant; SE = standard error; MMSE = Mini-Mental State Examination; HAM-D = Hamilton Depression Rating Scale

* Data missing in two participants