A Preliminary Study of fMRI-Guided rTMS in the Treatment of Generalized Anxiety Disorder

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Background: Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive method that holds promise for treating several psychiatric disorders. Yet the most effective location and parameters for treatment need more exploration. Also, whether rTMS is an effective treatment for individuals with a DSM-IV diagnosis of generalized anxiety disorder (GAD) has not been empirically tested. The goal of this pilot study was to evaluate whether functional magnetic resonance imaging (fMRI)–guided rTMS is effective in reducing symptoms of GAD.

Method: Ten participants with a DSM-IV diagnosis of GAD, recruited from the UCLA Anxiety Disorders Program, and between the ages of 18 and 56 years were enrolled in the study from August 2006 to March 2007. A pretreatment symptom provocation fMRI experiment was used to determine the most active location in the prefrontal cortex of the participants. Ten participants completed 6 sessions of rTMS over the course of 3 weeks, stereotactically directed to the previously determined prefrontal location. The primary efficacy measures were the Hamilton Rating Scale for Anxiety (HAM-A) and the Clinical Global Impressions-Improvement of Illness (CGI-I) scale. Response to treatment was defined as a reduction of 50% or more on the HAM-A and a CGI-I score of 1 or 2 ("very much improved" or "much improved," respectively).

Results: Overall, rTMS was associated with significant decreases in HAM-A scores ($t = 6.044$, $p = .001$) indicative of clinical improvement in GAD symptoms. At endpoint, 6 (60%) of the 10 participants who completed the study showed reductions of 50% or more on the HAM-A and a CGI-I score of 1 or 2; those 6 subjects also had an endpoint HAM-A score < 8, therefore meeting criteria for remission.

Conclusion: Results of the current study suggest that fMRI-guided rTMS treatment may be a beneficial technique for the treatment of anxiety disorders. Limitations include a small sample size and open-label design with a technology that may be associated with a large placebo response. These limitations necessitate further research to determine whether rTMS is indeed effective in treating anxiety disorders.

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One of the new treatment techniques that has emerged in recent years is repetitive transcranial magnetic stimulation (rTMS) of the brain.[1] Several companies are currently testing rTMS for U.S. Food and Drug Administration (FDA) approval for treatment of depression. The treatment has been approved in Canada and elsewhere as a safe and effective intervention. The rTMS procedure usually consists of delivering repetitive magnetic stimulation—at an intensity between 80% and 120% of the motor threshold—to the frontal or temporal lobes of the patient. The most frequently targeted location is the right prefrontal cortex, which is known to be associated with depression.[1]

The data on rTMS in anxiety disorders are limited and inconclusive. Research using animal models has shown that rTMS has antidepressant rather than antianxiety effects in rats.[2,3] Other research in rodents has shown that rTMS has both antidepressant and anxiolytic effects.[4] Repetitive TMS can be administered at low (0.3 to 1 Hz) or high (> 1 Hz) frequencies. Randomized clinical trials comparing high and low stimulation frequencies have shown that high-frequency rTMS is more effective in comorbid posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) than low-frequency rTMS.[5,6] Further, low-frequency rTMS has been shown to

be effective in individuals with PTSD without MDD.[7] Some evidence suggests that individuals with obsessive-compulsive disorder may also benefit from rTMS treatment.[5,8] Recent studies on the effects of rTMS treatment for panic disorder found moderate improvement in anxiety symptoms.[9–11] Despite the high prevalence and associated disability, to date there have been no investigations of the effects of rTMS treatment on symptoms of generalized anxiety disorder (GAD).[12]

The field of rTMS application to psychiatric conditions is in its beginning stages. To date, neither the optimal parameters nor locations of stimulation have been fully determined for rTMS treatment of any psychiatric condition. In most previously published studies, rTMS was administered to a cortical site at an arbitrary distance from the optimal motor stimulation site. In light of anatomical variability across brains, this approach is not ideal.[13]

An alternative approach is the use of meta-analysis data from imaging studies that allows the targeting of probabilistic locations of brain stimulation.[14] Unfortunately, recent reviews indicate that the circuits involved in anxiety or mood disorders are yet to be clearly defined.[15,16] Indeed, the few imaging studies of GAD that are available show a variety of activations in the prefrontal, orbital, and temporal cortex.[17] Furthermore, inter-participant variability in functional anatomy makes this probabilistic approach not optimal for selection of the best stimulation site.[13] These issues may explain some inconsistencies in clinical studies using rTMS.[1,8]

An exciting possibility for the study and advancement of rTMS treatment is its combination with neuroimaging.[18] Neuroimaging studies of rTMS effects are increasing, but results are still scarce despite the promise of this tool in studying brain response.[19] Several studies have attempted to use imaging guidance to target specific areas of the brain for the treatment of specific disorders.

Rossi et al.[20] applied slow rTMS to an epileptogenic area identified by functional magnetic resonance imaging (fMRI) and were able to reduce myoclonic seizures. Stereotactically guided rTMS has also been applied to the treatment of tinnitus.[21] Application of rTMS combined with an fMRI memory task showed improvement of memory in elderly patients with general memory complaints.[22] Several studies have shown that fMRI-guided targeting of areas of hallucinatory activation could be useful in temporary suppression of hallucinatory experience associated with schizophrenia.[23,24] Similar data were previously obtained using single-photon emission computed tomography (SPECT) scanning.[25] In addition, positron emission tomography–guided high-frequency rTMS treatment has shown to improve negative symptoms in a sample of individuals with schizophrenia in a randomized trial against sham treatment.[26] Another SPECT study demonstrated correlation between rTMS and cerebral blood flow during antidepressant response.[27] This study, however, did not use functional imaging data to guide the location of stimulation treatment.[27] Studies combining neuroimaging and rTMS have investigated the effects of different rTMS frequency. These studies have consistently shown that high-frequency rTMS increases cortical activity and low-frequency rTMS reduces it.[28,29] Low-frequency rTMS is considered to be the safest technique, as confirmed by several studies.[30]

On the basis of the above studies, we decided to conduct a pilot open trial to explore the feasibility of fMRI-guided treatment of GAD. In our study, we used an fMRI activation gambling task that has shown in previous studies to reliably produce cortical activation as well as some elevation in anxiety and apprehension in healthy individuals.[31] We then used frameless stereotaxy to apply low-frequency rTMS to the area identified by the fMRI as the most active and accessible to stimulation. The study had 2 hypotheses. First, we proposed that anxiety-inducing tasks would help us identify in individuals with GAD a critical area of activation within the prefrontal cortical areas that we could then use to target rTMS treatment. We further hypothesized that weekly sessions of image-guided slow (1 Hz) rTMS targeted to the identified area would have a significant effect on symptoms of GAD.

METHOD

This study was conducted in the UCLA Anxiety Disorders Program and in the UCLA Brain Mapping Division, which has a fully equipped fMRI and rTMS laboratory.

Study Design

This study utilized a 3-week open-label design to evaluate the efficacy of fMRI-guided rTMS in the treatment of GAD. Participants were recruited from August 2006 to March 2007 from the UCLA Anxiety Disorders Program at the Semel Institute for Neuroscience and Human Behavior, Los Angeles, Calif. Permission from UCLA's institutional review board was obtained to conduct this study. All eligible participants provided approved written consent prior to the initiation of any study-related procedure.

Participant Selection

Male or female participants aged 18 to 64 years were eligible if they had a current DSM-IV diagnosis of GAD. The Mini-International Neuropsychiatric Interview[32] was conducted at screening to confirm GAD diagnoses. Participants were eligible if they had a score greater than or equal to 18 on the Hamilton Rating Scale for Anxiety[33] (HAM-A) and less than 17 on the 17-item Hamilton Rating Scale for Depression[34] (HAM-D) at baseline. We included participants with lower HAM-A scores than have typically been used in GAD clinical trials (i.e., HAM-A

score > 20) so that our results could be generalized to include the numerous participants with more mild GAD symptomatology.[35]

Participants were excluded if they had a primary diagnosis meeting DSM-IV criteria for any Axis I disorder other than GAD, as were participants who met DSM-IV criteria for mental retardation or any pervasive developmental disorder or who had a neurologic impairment. Also excluded were those with a current diagnosis or recent (6-month) history of drug or alcohol dependence or abuse, current suicidal ideation and/or history of suicide attempt, or any personality disorder of sufficient severity to interfere with participation in the study. Other exclusion criteria included the presence or history of a medical disease that might put the individual at risk or compromise the study. Pregnant or breastfeeding women and those of childbearing potential who were not practicing a reliable form of contraception were also excluded from the study.

Participants were not permitted use of any psychotropic medications, with the exception of stable doses of serotonin reuptake inhibitors, for at least 3 months prior to enrollment. Participants who used as-needed benzodiazepines were permitted to enter the study and to receive rTMS treatment if the frequency of use did not exceed 2 times per week. They were not permitted to use these medications 2 days prior to the fMRI experiment or 2 days prior to their appointment for rTMS treatment.

Functional MRI

We first used fMRI during the gambling task to localize anxiety-related brain activations in each individual participant and then used this information to guide treatment with rTMS.

Gambling task. In order to produce anxiety, we gave participants in the fMRI scanner a computerized gambling game that involved uncertainty and frustration. Participants were told before the scans that they would be given $50 and had the opportunity to win more money or lose their money, depending on their performance in the gambling game. On each trial, the participant made a prediction about the color of a card drawn from a deck. Two cards, 1 red and 1 blue, appeared on the screen with the text "please choose a card." By pressing 1 of 2 buttons, the participants chose a red or a blue card. Then a card was "drawn" from the deck, appearing underneath the 2 choice cards. If the color of this card matched the participant's choice, he or she was rewarded with $5, if the color did not match, $5 was taken away. After each card was drawn, a sentence appeared telling the participant how much money he or she currently had. Each trial lasted 6 seconds, and trials were grouped into 48-second blocks containing 8 trials each. Each functional scan began with a 12-second rest, followed by 4 task blocks. Each task block was followed by a 32-second rest period during which only fixation crosses remained on the screen.

During half of the blocks ("low uncertainty"), the participants were informed that the deck consisted of 50% red cards and 50% blue cards, which would tell them there was a 50% chance of being correct each time. This was communicated by the number 50 appearing above each of the choice cards. During these blocks, the outcome was arranged to ensure that half of the participant's choices were rewarded. In other blocks ("high uncertainty"), we replaced these numbers with question marks. In these blocks, participants were told that the proportion of red or blue cards in the deck could be anything. Also, during these "high uncertainty" blocks, the outcome was fixed so that participants would lose money 6 out of 8 times.

Each participant completed 3 functional runs, which each contained 2 "low uncertainty" and 2 "high uncertainty" blocks. The money won or lost carried over from block to block and from scan to scan, so that by the last scan, all participants had lost all of their money.

Image acquisition. Images were acquired using a Siemens Allegra 3.0 T MRI scanner (Siemens, Malvern, Pa.). Two sets of high-resolution anatomical images were obtained for registration purposes. We acquired a magnetization-prepared rapid gradient echo (MP-RAGE) (TR = 2300, TE = 2.93, flip angle = 8°) with 160 sagittal slices, each 1 mm thick with a .5-mm gap and 1.33-mm × 1.33-mm in-plane resolution. We also acquired a T2-weighted coplanar image (TR = 5000, TE = 33, flip angle = 90°) with 36 transverse slices covering the whole brain, each 3 mm thick with a 1-mm gap, a 128 × 128 matrix, and an in-plane resolution of 1.5 mm × 1.5 mm.

Each functional run involved the acquisition of 166 blood-oxygen-level-dependent (BOLD)–weighted echoplanar volumes (TR = 2000, TE = 25, flip angle = 90°), each with 36 transverse slices, 3 mm thick, a 1-mm gap, and a 64 × 64 matrix yielding an in-plane resolution of 3 mm × 3 mm. A functional run lasted 5 minutes and 32 seconds, and each participant completed 3 functional runs.

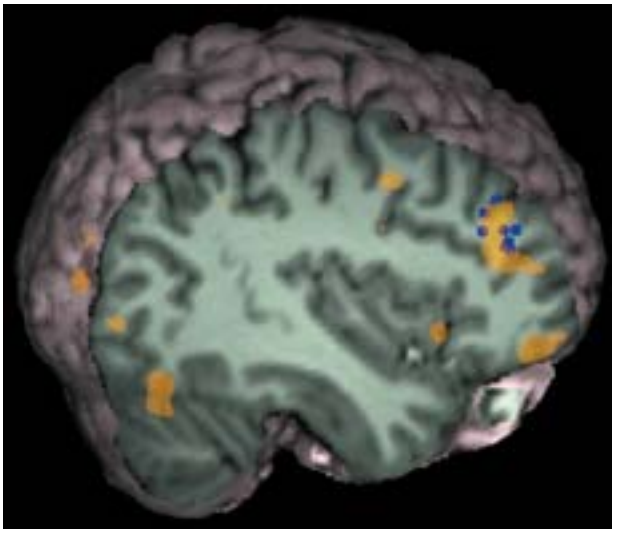
fMRI data analysis. Analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.1, part of FSL (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain [FMRIB] Software Library, www.fmrib.ox.ac.uk/fsl). After motion correction, images were smoothed using an 8-mm Gaussian full-width half-maximum algorithm in 3 dimensions and temporally high-pass filtered with a cutoff period of 75 seconds.[36] The BOLD response was modeled using a separate explanatory variable for each of the 2 conditions, "low uncertainty" and "high uncertainty." For each stimulus type, the presentation design was convolved with a gamma function to produce an expected BOLD response. The temporal derivative of this time course was also

included in the model for each explanatory variable. Data were then fitted to the model using FSL's implementation of the general linear model. For each participant, statistical maps were obtained for each of the 3 runs, then a fixed-effects analysis across these 3 runs was performed. The rTMS procedure for each individual was guided based on these participant-level data.

We used FMRIB's Linear Image Registration Tool to register the functional data to the high-resolution MP-RAGE anatomical image for each participant as well as to the standard Montreal Neurological Institute (MNI) atlas for the purposes of group statistics.[36] Functional images were aligned with the high-resolution coplanar T2-weighted image using a 6 degree-of-freedom, rigid-body warping procedure, and this coplanar volume was then registered to the T1-weighted MP-RAGE using a 6 degree-of-freedom, rigid-body warp. Finally, the MP-RAGE was registered to the standard MNI atlas with a 12 degree-of-freedom affine transformation.

Random-effects group-level analysis (across all participants) was carried out using FMRIB's Local Analysis of Mixed Effects.[37] The z (Gaussianized t and f) statistic images were thresholded using clusters determined by z greater than 2.3 and a (corrected) cluster significance threshold of p = .01.[38–40] These group-level data were not used in the rTMS treatment and only served to examine the consistency of the task-related brain activations.

Figure 1. Task-Related fMRI Signal Changes and rTMS Target Location (blue dots)[a]



[a]The gambling task showed significant signal changes in the right dorsolateral prefrontal cortex. Peak activation of the group data was located at 42, 36, 32 in the middle frontal gyrus. Each blue dot represents the peak activation of an individual subject. Group data are shown in yellow.
Abbreviations: fMRI = functional magnetic resonance imaging, rTMS = repetitive transcranial magnetic stimulation.

rTMS Procedure

Comparison between the "high uncertainty" and "low uncertainty" conditions did not yield significant brain activations in any participant. Because the monetary losses carried over from block to block, frustration and uncertainty may have remained high throughout the task. Thus, we chose the rTMS target location from the activation across all task periods compared with rest. Every participant showed a significant cluster of activation in the right prefrontal cortex (see fMRI Results for details). We chose each participant's peak voxel in the right prefrontal cortex as the target for rTMS. This site of stimulation was located on the participant's head using the BrainSight system for frameless stereotaxy (Rogue Research, Montreal, Canada). This system allows us to visualize the position of the rTMS coil in 3-D space relative to the high-resolution anatomical MRI of the participant's brain.

Participants completed 6 sessions of rTMS. The sessions were conducted twice a week for 3 weeks. Repetitive TMS was applied using a Magstim Rapid Stimulator (Magstim, Spring Gardens, U.K.) with a figure-of-8 coil (outer diameter 9 cm). At the start of each session, we measured the active and resting motor threshold by stimulating over the primary motor cortex to cause twitches in the first dorsal interosseous muscle. Threshold was defined as the minimum percentage of stimulator output that produced a visible twitch 50% of the time.

Repetitive TMS was delivered to the target site at a frequency of 1 Hz for 15 minutes (900 total pulses). The intensity of the rTMS was set to 90% of the passive motor threshold for each participant.

Assessment of the Treatment Outcome

Psychiatric assessments included the HAM-A,[33] the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales,[41] and the 17-item HAM-D.[34] In addition, individuals completed the Individuals Global Impression of Improvement Scale[41] and the Four-Dimensional Anxiety and Depression Scale[42] (FDADS).

The FDADS is a self-rated measure of anxiety and depression that has been tested in the general population as well as in clinical samples and demonstrates sound psychometric properties with good internal consistency and test-retest reliability. The scale has demonstrated validity relative to other measures of anxiety and depression.[42–45] Safety measures included the initial and final physical and routine laboratory evaluations (i.e., electrolytes, hematology, and urinalysis) and subjective reports on the Side Effects Checklist.[46]

Statistical Methods

The primary efficacy measures included the CGI-I and HAM-A. Response to treatment was defined as a reduction

Table 1: Demographic and Clinical Characteristics of the Study Sample (N = 10)

Patient Number	Gender	Age, y[a]	HAM-A Baseline Score[b]	HAM-A Endpoint Score[c]	HAM-D Baseline Score[d]	HAM-D Endpoint Score[e]	FDADS-Anxiety Baseline Score[f]	FDADS-Anxiety Endpoint Score[g]	CGI-I Endpoint Score
1	Female	56	40	0	13	0	36	12	1*
2	Male	34	17	2	13	0	24	15	1*
3	Male	54	31	11	15	3	30	18	3†
4	Male	56	28	22	13	8	43	22	4
5	Male	47	22	11	8	6	34	26	3†
6	Female	55	24	3	7	1	35	29	1*
7	Male	38	30	19	11	6	27	18	4
8	Female	47	19	0	3	0	23	13	1*
9	Female	48	19	3	5	4	22	15	1*
10	Female	18	18	2	4	0	28	17	1*

[a]Mean ± SD age = 45.30 ± 12.1 years.
[b]Mean ± SD score = 24.80 ± 7.37.
[c]Mean ± SD score = 7.30 ± 8.02, t = 6.044, p = .001.
[d]Mean ± SD score = 9.20 ± 4.34.
[e]Mean ± SD score = 2.80 ± 3.04, t = 4.42, p = .001.
[f]Mean ± SD score = 30.20 ± 6.72.
[g]Mean ± SD score = 18.5 ± 5.56, t = 6.16, p = .000.
*Patients who met criteria for remission.
†Patients who significantly improved (50% decrease in HAM-D scores) but did not meet criteria for remission.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement of Illness scale, FDADS = Four-Dimensional Anxiety and Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression.

of 50% or more on the HAM-A, and symptom remission was defined as a CGI-I score of 1 or 2 ("very much improved" or "much improved," respectively) and a score less than or equal to 8 on the HAM-A. Data were entered anonymously into an Excel spreadsheet and analyzed by the UCLA Semel Institute Statistical Core. The analysis was done on the intent-to-treat sample using last observation carried forward. A 1-sample paired t test was used to compare endpoint to baseline means on the HAM-A, with a significance level set at $\alpha = .05$, 2-tailed.

RESULTS

fMRI Results

Comparison of the gambling task versus rest in our mixed-effects group analysis revealed widespread activations throughout the brain, including the occipital cortex, the intraparietal region bilaterally, the premotor cortex bilaterally, and the dorsolateral prefrontal cortex (DLPFC) on the right side. The right DLPFC was our intended site of stimulation. In the group data, the peak voxel in the right DLPFC was located in the middle frontal gyrus at 42, 36, 32 with a z value of 4.99 ($p < 10^{-7}$). Every participant showed a significant cluster of activity in this region (Figure 1).

rTMS Treatment Results

Fifteen participants expressed interest in the study and engaged in an initial telephone screen. Thirty-four percent of participants (N = 5) were deemed ineligible to participate. Reasons for ineligibility included excluded psychotropic medication (N = 3, 60%) and excluded psychiatric condition (N = 2, 40%). Ten participants enrolled in the study and received rTMS treatment. The mean ± SD age of the sample was 45.30 ± 12.1 years. Of the 10 individuals enrolled in the study, 5 (50%) were women and 5 (50%) were men. Three participants (30%) had been taking psychotropic medications (serotonin reuptake inhibitors) for at least 3 months prior to enrollment and continued throughout the study. Overall, 100% of individuals (N = 10) completed the study.

Mean ± SD HAM-A scores decreased significantly from baseline (24.80 ± 7.37) to endpoint (7.30 ± 8.02) (t = 6.044, p = .001) (Table 1). Mean ± SD HAM-D scores changed significantly from 9.20 ± 4.34 at baseline to 2.80 ± 3.04 at endpoint (t = 4.42, p = .001). Mean ± SD FDADS anxiety subscale scores changed significantly from 30.20 ± 6.72 at baseline to 18.5 ± 5.56 at endpoint (t = 6.16, p = .000). Six of the individuals had a dramatic improvement reaching remission (defined as a score ≤ 8 on the HAM-A and a score of 1 or 2 on the CGI-I) within the 3 weeks of treatment. Two more participants had more than 50% decreases in their HAM-A scores but did not meet remission criteria.

DISCUSSION

Results of the present study demonstrate that low-frequency rTMS treatment administered with frameless stereotaxy on the basis of individual functional imaging data significantly decreases anxiety symptoms associated with GAD. Every participant who entered this study had improvement in their anxiety. Significant improvements were seen both on clinician-rated (HAM-A) and patient-rated (FDADS anxiety) scales.

Individuals also described improvement in associated symptoms (i.e., depression and insomnia) that was observable after a single treatment in some individuals. For

example, participant 1 had anxiety and insomnia that was for many years unsuccessfully treated with multiple trials of medications and therapy. After the first treatment, he had a dramatic improvement in the quality of his sleep and eventually experienced resolution of his anxiety and worry. In addition, 9 of the 10 individuals achieved depression remission criteria of a HAM-D score less than or equal to 7, although the sample had low baseline levels of depression (mean ± SD HAM-D score of 9.20 ± 4.34).

Limitations of the study include a small sample size and the fact that it was an open trial, which is often associated with a stronger response than with a controlled trial.[47] In addition, a sophisticated technological pretreatment and treatment manipulation (i.e., fMRI and rTMS) could have enhanced the placebo response. A sham-controlled study could help to resolve this issue.

The usefulness of fMRI guidance of the treatment also needs to be further explored. While we were able to identify foci of activation for each participant individually, they all clustered in the right prefrontal area (see Figure 1).

Previous studies of low-frequency rTMS administered to the right prefrontal area in individuals with PTSD and panic disorder showed improvements in anxiety.[7,9,11] Also, a study using masked/unmasked face paradigm determined that low-frequency rTMS applied to the right prefrontal cortex influenced emotional processing.[48] Therefore, the effect of fMRI guidance of rTMS in our study could be nonspecific given that rTMS has a large focus spreading effect that can influence a relatively extensive cortical area. A study comparing the effect of fMRI guidance to a nonspecific prefrontal location of rTMS coil could address this issue. There have been very few other functional neuroimaging studies in GAD with which to compare the activated networks in this study.[49–51] There have been even fewer symptom-provocation studies in GAD.[52,53]

Wu et al.[51] examined both resting and arousal states in a PET study of GAD individuals. With arousal tasks, they found increased metabolic activity in the basal ganglia and the right parietal cortex.[51] Hoehn-Saric et al.,[52] in a worry symptom provocation fMRI study, found activation in medial prefrontal and thalamostriatal regions that was reduced after treatment with citalopram. Monk et al.,[53] in a group of adolescents with GAD, found right ventral prefrontal activation when exposed to angry faces. As these previous studies used very different symptom provocation tasks, and no study used the same gambling task, it is difficult to compare results.

Many previous studies of healthy controls have found that the prefrontal region, the right DLPFC (BA 9), which was activated in all 10 participants in this study, is involved in sustained attention across a variety of tasks (see Cabeza and Nyberg[54] for review). It is possible that the gambling task in this study activated a region that mediates attention and vigilance. In GAD, this region may be relevant to the evaluation and response to threatening information. Whether this region and associated networks are hyperactive relative to controls for this task and whether they decrease in activity after rTMS treatment would need to be examined in future studies. In summary, it is unclear if the gambling task/fMRI probe used in this study resulted in activation specific to GAD.

Despite shortcomings characteristic of small clinical trials, this study demonstrated the feasibility and robust preliminary efficacy of fMRI-guided rTMS in individuals with chronic GAD. Further sham-controlled studies could explore the true efficacy magnitude of this treatment. Future studies should also address the durability of the response; from the limited treatment duration of 3 weeks in this study, it remains unknown if the observed improvements are long lasting or if individuals need to continue maintenance treatments.

The concept of individualized fMRI guidance for rTMS treatments may prove to be very useful, given the likely heterogeneity of pathophysiological abnormalities of clinical samples defined by the DSM-IV. These preliminary results therefore warrant exploration in future, controlled studies.

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