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Therapeutic High-Frequency Repetitive Transcranial Magnetic Stimulation Concurrently Improves Mood and Anxiety in Patients Using Benzodiazepines

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Objectives/Hypothesis: In this study, we tested the use of repetitive transcranial magnetic stimulation (rTMS) to reduce depression and anxiety in patients using or not using benzodiazepines. We hypothesized that rTMS would concurrently reduce symptoms in both depression and anxiety and that these reductions would correlate with patients using benzodiazepines.

Materials and Methods: This retrospective study screened for patients treated in a TMS clinic within a five-year period. Each patient had received high-frequency (10 or 20 Hz) rTMS over the left dorsolateral prefrontal cortex and completed pre- and posttreatment Beck Depression Inventory and Visual Analog Scale-Anxiety ratings. Fifty-eight patients (37 women) met these criteria and 37 (63.8%) took benzodiazepines. We used two mixed analysis of variance analyses to separately evaluate the effects of rTMS on depression and anxiety. We additionally directly evaluated the relationship between reductions in depression and anxiety by computing three linear correlations (all patients, benzodiazepine users, nonbenzodiazepine users).

Results: rTMS was an effective treatment of depression for all patients ($p < 0.001$). rTMS also reduced anxiety scores from pre- to posttreatment ($p = 0.002$). Furthermore, reductions in depression and anxiety were correlated ($p = 0.002$). These changes in depression and anxiety only correlated with benzodiazepine users ($p < 0.001$) and not nonbenzodiazepine users ($p = 0.608$).

Conclusions: rTMS concurrently improved both depression and anxiety, and changes in these measures correlated with patients using benzodiazepines. With further investigation, rTMS may be a helpful treatment for both anxiety and depression simultaneously.

Keywords: Anxiety, anxious depression, benzodiazepines, depression, TMS

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INTRODUCTION

Depression and anxiety are strongly associated, with an estimated comorbidity rate of 50–80% (1–3). The field of psychiatry is increasingly acknowledging of this relationship, as seen in the Diagnostic and Statistical Manual 5's (DSM-5) recent incorporation of an "anxious distress" specifier within its definition of major depressive disorder (4). The neurobiology of depression and anxiety disorders are also linked (5). Despite a growing body of evidence showing the relationship between depression and anxiety, there remains a need for concurrently treating both symptom clusters.

Repetitive Transcranial magnetic stimulation (rTMS) is Food and Drug Administration (FDA) cleared to treat pharmacoresistant depression (6,7). However, much remains unknown about the relationship between changes in mood and anxiety from rTMS treatment. A handful of prior retrospective studies have demonstrated that rTMS can improve both mood and anxiety, but conclusions are limited by the lack of correlation between the two variables (8,9). A further limitation is both studies' use of the Hamilton Psychiatric Rating Scale for Depression (HAM-D) to assess changes in mood from TMS. Using the HAM-D as a depression inventory for research also evaluating anxiety on other scales is problematic due to the potential co-linearity of any anxiety reductions on both depression and anxiety scales driving any observed effect. In fact, Diefenbach et al. (8) used the anxiety subscores of the HAM-D (8) and White and Tavakoli (9) used the 7-item Generalized Anxiety Disorder scale (9).

In this study, we aimed to replicate Diefenbach et al. (8) and White and Tavakoli's (9) findings using the Beck Depression Inventory (BDI), a commonly used mood assessment that does not evaluate anxiety. Furthermore, we wanted to directly evaluate how these symptoms improve in relation to one another at the group level by

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statistically correlating improvements in mood with improvements in anxiety in patients using or not using benzodiazepines, which we used as a surrogate marker of anxiety. We hypothesized that changes in depression and anxiety would concurrently improve and would correlate with patients using benzodiazepines.

MATERIALS AND METHODS

Participants

This protocol was approved by Beth Israel Deaconess' Institutional Review Board. Our inclusion criteria were patients treated with therapeutic high-frequency rTMS for depression over the left dorsolateral prefrontal cortex (DLPFC) who completed pre- and posttreatment BDI and Visual Analog Scale-Anxiety (VAS-A) ratings. Fifty-eight participants (37 women) met these criteria and had an average age of 51.9 (range = 18–80). Of the 58 participants, 37 (63.8%) regularly used benzodiazepines, which we used as a surrogate marker for psychopathologic anxiety that remained despite trials of antidepressants. Benzodiazepines and other medications were kept constant throughout the rTMS treatment. In addition, no patients started any medications during the rTMS treatment course.

Measure of Depression: Beck Depression Inventory

The BDI is a commonly used, well-validated, and self-reported outcome measure for depressive symptoms (10). Participants rated 21 groups of statements on scales of 0 to 3, with higher scores corresponding to more severe depression. We chose to use the BDI as it does not evaluate anxiety. In contrast, the HAM-D scores two anxiety-related indices ("Anxiety Psychic" and "Anxiety Somatic").

Measure of Anxiety: Visual Analog Scale for Anxiety

The VAS-A is a continuous-variable, self-reported measure of generalized anxiety disorder. Participants marked a line to indicate their current levels of anxiety on a scale from "Not at all anxious" (A score of 0) to "Extremely Anxious" (a score of 10). Prior research has demonstrated that the VAS-A validly and reliably measures anxiety in comparison with physician-administered assessments of anxiety such as the Hamilton Rating Scale for Anxiety and the Hospital Anxiety and Depression Scale—Anxiety subscale (11).

Experimental Procedure

For each participant, trained TMS technicians acquired each patient's self-reported pre-BDI and pre-VAS-A measures prior to the start of the first treatment. The TMS technicians also acquired each patient's post-BDI and post-VAS-A measures prior to the last session.

rTMS Parameters

The TMS clinic used the FDA-cleared Neuronetics NeuroStar TMS Therapy System (Malvern, PA, USA) and the FDA-cleared Magstim Rapid2 device (Carmarthenshire, West Wales, UK). Patients were split roughly evenly between devices (58.6% on Neuronetics and 41.4% on Magstim). All participants received high-frequency rTMS (10 Hz for 3000 pulses per treatment session or 20 Hz for 1600 pulses per treatment session) over the left DLPFC. Trained TMS technicians targeted the DLPFC using the standard approach of positioning the coil 5.5 cm anterior of the motor threshold hotspot. Patients completed an average of 21.6 treatment sessions (SD = 5.99, range = 10–30). Patients were not separately analyzed by TMS machine as it does not impact treatment outcome.

Statistical Analysis

We used two mixed-factor analysis of variance tests (ANOVAs) to examine changes in mood and anxiety. A 2 (time of BDI: pretreatment, posttreatment) × 2 (benzodiazepine use: yes, no) ANOVA evaluated the effects of the treatment and benzodiazepine use on mood. Similarly, we used a 2 (time of VAS-A: pre, post) × 2 (benzodiazepine use: yes, no) ANOVA to test how the treatment changed patients' anxiety.

We additionally calculated three Pearson's correlations (all patients [N = 58], benzodiazepine users [N = 37], and nonbenzodiazepine users [N = 21]) to directly evaluate the relationship between changes in mood and changes in anxiety. Changes in mood were calculated as a percent change in BDI from pre- to posttreatment. Change in VAS-A was computed as a point reduction from the start to the end of the treatment (e.g., a participant who had a pretreatment VAS-A of 10 and posttreatment VAS-A of 2 would have a change in VAS-A of 8). All analyses were conducted in SPSS 25.0.

RESULTS

BDI Scores Significantly Improve From Pre- to Posttreatment in Both Groups

BDI scores significantly decreased from pretreatment (M = 31.8, SD = 10.7) to posttreatment (M = 20.4, SD = 12.7), $F_{1,56}$ = 35.8, $p < 0.001$, η_p^2 = 0.39. There was no interaction between BDI scores and benzodiazepine use, indicating that BDI dropped similarly for both groups, $F_{1,56}$ = 0.12, p = 0.731, η_p^2 = 0.002.

VAS-A Scores Significantly Improve From Pre- to Posttreatment in Both Groups

In all patients, VAS-A significantly decreased from pretreatment (M = 5.92, SD = 2.45) to posttreatment (M = 4.69, SD = 2.73), $F_{1,56}$ = 10.1, p = 0.002, η_p^2 = 0.15. Pretreatment, benzodiazepine users (M = 6.57, SD = 2.18) were significantly more anxious than non-benzodiazepine users (M = 4.79, SD = 2.54), t_{56} = −2.81, p = 0.007, validating benzodiazepine use as a surrogate marker for high anxiety. Posttreatment, there remained a significant difference between benzodiazepine users (M = 5.36, SD = 2.61) and nonbenzodiazepine users (M = 3.51, SD = 2.60), t_{56} = −2.60, p = 0.012. While TMS did not reduce the anxiety of benzodiazepine users to the level of nonbenzodiazepine users, it did significantly improve anxiety for patients using benzodiazepines.

BDI and VAS-A Scores Significantly Correlate for Patients Using Benzodiazepines

We found a significant relationship between changes in BDI and VAS-A scores such that greater percentage improvements in mood tended to be accompanied by greater improvements in anxiety, R = 0.39, N = 58, p = 0.002 (Fig. 1a). Two further correlations showed that improvement in depression was related to improvement in anxiety only for patients using benzodiazepines, R = 0.55, N = 37, $p < 0.001$ (Fig. 1b) and not for patients who were not using benzodiazepines, R = 0.12, N = 21, p = 0.608 (Fig. 1c). Removal of a potential non-benzodiazepine outlier (VAS-A change of −5.1 and BDI change of 94.9%) did not change the correlative significance of mood and anxiety changes in non-benzodiazepine users, R = 0.39, N = 20, p = 0.093. Therefore, mood and anxiety changes are statistically related only in patients using benzodiazepines, although this

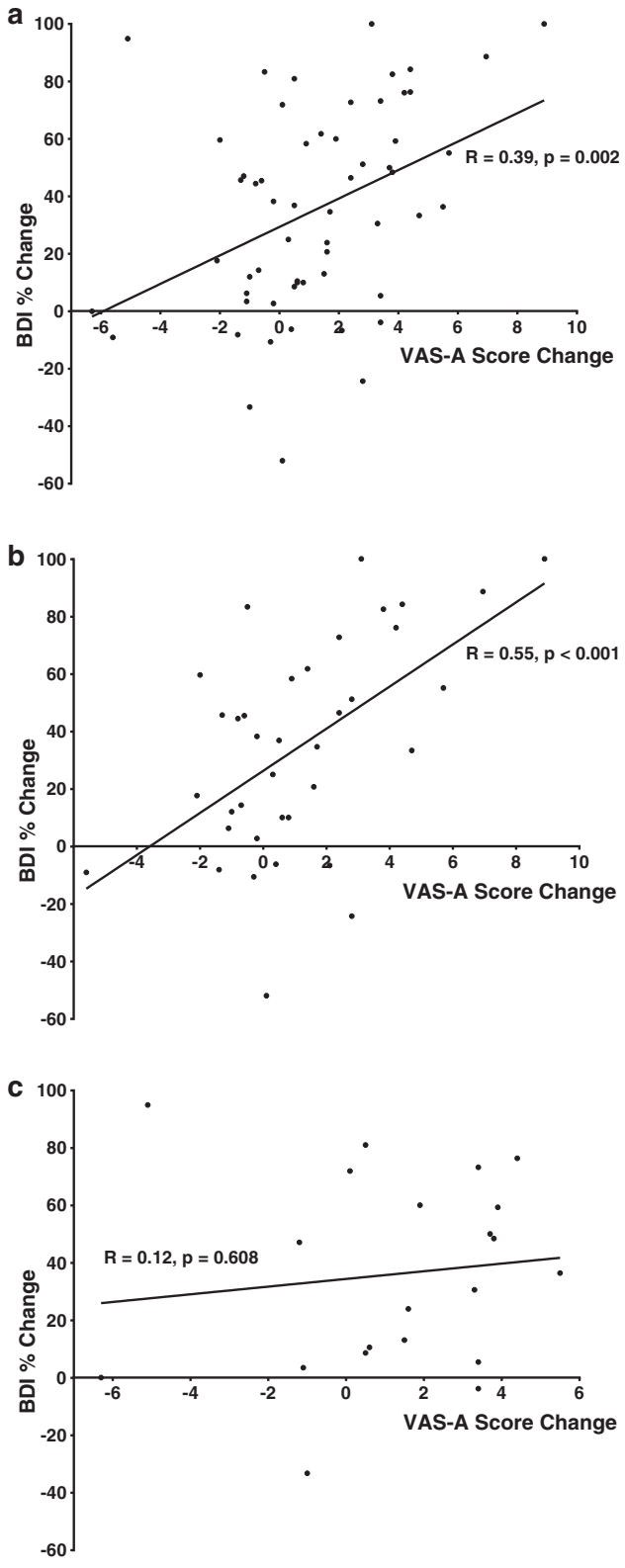

Figure 1. a. rTMS over the left DLPFC simultaneously improved anxiety and depression (p = 0.002). b. For benzodiazepine users, rTMS concurrently improved mood and anxiety ($p < 0.001$). c. For non-benzodiazepine users, rTMS improved patients' moods. However, improvements in mood and anxiety did not correlate (p = 0.608).

could be due to a floor effect for non-benzodiazepine users as they started with lower VAS-A scores.

DISCUSSION

This study substantiates prior findings that rTMS for treatment-resistant depression can improve both depressive and anxious symptoms (8,9). Unlike the existing literature that relied upon physician-administered assessments, we chose to use self-report measures of mood (BDI) and anxiety (VAS-A). Our choice of using these measures was particularly informed by reducing the possibility of collinearity between scales driving any potential correlation between improvements of depression and anxiety.

We additionally report a novel finding not only that rTMS over the DLPFC can separately improve mood and anxiety, but also that these measures correlate with patients using benzodiazepines. With further investigation, rTMS over the left DLPFC may potentially be a treatment approach that can simultaneously be helpful in both symptom clusters, particularly at the group level. One explanation for this phenomenon may arise from the prefrontal cortex also being a neuromodulator of connectivity networks involved in anxiety (12).

There were several limitations to this study. It was retrospective in nature, and patients were not screened for anxiety disorders or other mental health conditions beyond an initial psychiatric interview, which primarily focused on the diagnosis of depression. We used the presence of current benzodiazepine usage as markers for anxiety, understanding that these measures are inherently limited even after statistical validation. The conclusions of this study would also be strengthened by recording the specific medications and dosages patients took as well as having follow-up assessments of benzodiazepine use to evaluate if rTMS led to decreased usage. It would be useful to expand this study and attempt to replicate its findings in a prospective manner with a structured diagnostic interview under the premise of the new DSM-5 diagnostic criteria.

CONCLUSIONS

rTMS concurrently improved both depression and anxiety. These measures were correlated with benzodiazepine users. With further investigation, rTMS may be a helpful treatment for both anxiety and depression simultaneously.

Authorship Statement

Kevin A. Caulfield designed the study, conducted the data analyses, made the figures, and wrote the manuscript. Adam P. Stern designed the study and wrote the manuscript.

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REFERENCES

1. De Graaf R, Bijl R, Spijker J, Beekman A, Vollebergh W. Temporal sequencing of lifetime mood disorders in relation to comorbid anxiety and substance use disorders. *Soc Psychiatry Psychiatr Epidemiol* 2003;38:1–11.
2. Spinhoven P, van Balkom A, Nolen WA. Comorbidity patterns of anxiety and depressive disorders in a large cohort study: the Netherlands Study of Depression and Anxiety (NESDA). *J Clin Psychiatry* 2011;72: 341–348.
3. Kessler RC, McGonagle KA, Zhao S et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;51:8–19.
4. Penninx BW. Depression and anxiety: their insidious dance. *Lancet Psychiatry* 2015;2:479–480.
5. Ionescu DF, Niciu MJ, Mathews DC, Richards EM, Zarate CA Jr. Neurobiology of anxious depression: a review. *Depress Anxiety* 2013;30:374–385.
6. O'Reardon JP, Solvason HB, Janicak PG et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* 2007;62:1208–1216.
7. Levkovitz Y, Isserles M, Padberg F et al. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. *World Psychiatry* 2015;14:64–73.
8. Diefenbach GJ, Bragdon L, Goethe JW. Treating anxious depression using repetitive transcranial magnetic stimulation. *J Affect Disord* 2013;151:365–368.
9. White D, Tavakoli S. Repetitive transcranial magnetic stimulation for treatment of major depressive disorder with comorbid generalized anxiety disorder. *Ann Clin Psychiatry* 2015;27:192–196.
10. Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck depression inventory: twenty-five years of evaluation. *Clin Psychol Rev* 1988;8:77–100.
11. Williams VSL, Morlock RJ, Feltner D. Psychometric evaluation of a visual analog scale for the assessment of anxiety. *Health Qual Life Outcomes* 2010;8:57.
12. Bishop S, Duncan J, Brett M, Lawrence AD. Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. *Nat Neurosci* 2004;7:184–188.

