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# Improvements in emotion regulation following repetitive transcranial magnetic stimulation for generalized anxiety disorder

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ABSTRACT

Generalized anxiety disorder (GAD) is characterized by emotion regulation difficulties, which are associated with abnormalities in neural circuits encompassing fronto-limbic regions including the dorsolateral prefrontal cortex (DLPFC). The aim of this study was to determine whether DLPFC neuromodulation improves emotion regulation in patients with GAD. This is a secondary analysis from a randomized-controlled trial comparing 30 sessions of low-frequency right-sided active ($n = 13$) versus sham ($n = 12$, sham coil) repetitive transcranial magnetic stimulation (rTMS) at the right DLPFC in patients with GAD. Results indicated statistically significant improvements in self-reported emotion regulation difficulties at posttreatment and 3-month follow-up in the active group only. Improvements were found primarily in the domains of goal-directed behaviors and impulse control and were significantly associated with a global clinician rating of improvement. These preliminary results support rTMS as a treatment for GAD and suggest improved emotion regulation as a possible mechanism of change.



## 1. Introduction

Generalized anxiety disorder (GAD) is characterized in part by deficits in the identification and regulation of emotional experiences. The emotion regulation model of GAD (Mennin, Heimberg, Turk, & Fresco, 2002) proposes that these deficits contribute to a process of excessive emotional arousal and subsequent maladaptive emotion regulation strategies which serve to maintain symptoms and associated impairments. Specifically, patients with GAD experience difficulties with emotion intensity, labeling, expression, acceptance, and modulation (e.g., Mennin, Heimberg, Turk, & Fresco, 2005; Salters-Pedneault, Roemer, Tull, Rucker, & Mennin, 2006). Cognitive-behavioral (Mennin, 2004) and acceptance-based (Roemer & Orsillo, 2002) psychological therapies have been developed to target emotion regulation deficits as a treatment for patients with GAD. The aim of the current study was to determine whether neuromodulation may also improve emotion regulation deficits in patients with GAD.

Recent evidence from neuroimaging studies has strongly suggested that emotion regulation is subserved by a specific neural circuit, including fronto-limbic regions (Ochsner, Silvers, & Buhle, 2012), and abnormalities in this neural circuitry have been found in patients with GAD. For example, during worry induction patients with GAD demonstrate stronger connectivity between limbic and prefrontal regions relative to healthy control (HC) volunteers (Andreescu et al., 2014, 2015). In addition, patients with GAD are unable to inhibit worry-related neural activity once a worry induction task is completed (Paulesu et al., 2010). While completing emotion modulation tasks (e.g., reappraisal, suppression) patients with GAD demonstrate hypoactivation of prefrontal and/or anterior cingulate cortex (Andreescu et al., 2011; Ball, Ramsawh, Campbell-Sills, Paulus, & Stein, 2013), and less connectivity of the medial prefrontal cortex with prefrontal regions (specifically the dorsolateral prefrontal cortex [DLPFC]) and limbic regions (e.g., insula) than HC volunteers (Andreescu et al., 2015). During an emotional conflict task requiring implicit emotion regulation, patients with GAD also fail to engage the anterior cingulate cortex – a brain region associated with successful conflict resolution and emotion inhibition – relative to HC volunteers (Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010).

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Neuromodulation using repetitive transcranial magnetic stimulaton (rTMS) is superior to sham in the treatment of depression (Berlim, Van den Eynde, & Jeff Daskalakis, 2013; Kedzior, Azorina, & Reitz, 2014), and evidence suggests that anxiety symptoms may also improve in depressed patients receiving neuromodulation therapies (Berlim, McGirr, Beaulieu, & Turecki, 2011; Diefenbach, Bragdon, & Goethe, 2013; Kedzior, Gellersen, Roth, & Zangen, 2015). Uncontrolled research has indicated that neuromodulation of the DLPFC improves anxiety symptoms in patients with GAD (Bystritsky et al., 2008; Shiozawa et al., 2014) and we have recently reported that in a randomized controlled trial (RCT) active DLPFC neuromodulation was superior to sham for improving GAD symptoms (Diefenbach et al., in press). Some research suggests that pharmacotherapy improves connectivity between the DLPFC and prefrontal regions during emotion regulation in patients with GAD (Andreescu et al., 2015). However, the extent to which DLPFC neuromodulation improves emotion regulation deficits in patients with GAD has not been explored.

This study reports secondary analyses from the RCT mentioned above comparing active versus sham rTMS of right DLPFC in patients with GAD (Diefenbach et al., in press). Participants completed the Difficulties in Emotion Regulation Scale (DERS, Gratz & Roemer, 2004) at pretreatment, posttreatment, and 3-month follow-up. The DERS contains six subscales, each assessing different facets of emotion regulation (e.g., awareness, impulse control), and the subscales are combined for a total score. It was hypothesized that patients receiving active versus sham rTMS would report more improvements in emotion regulation as assessed by the DERS total score and that improvement in emotion regulation would be associated with treatment response. Additional exploratory analyses were conducted on the DERS subscales to determine whether treatment effects were pervasive or specific to certain aspects of emotion regulation.

## 2. Material and methods

### 2.1. Participants

Participants were recruited from an outpatient clinic and the community (e.g., newspaper advertisements, Internet) for a RCT comparing active to sham rTMS in adult outpatients diagnosed with GAD (Diefenbach et al., in press). Thirty-four participants enrolled; however, eight withdrew prior to randomization, and data from one participant was excluded due to treatment schedule violation. Thus, twenty-five participants ($n = 13$ active; $n = 12$ sham) were included in data analyses. Participants in both groups reported a mean age of 44 (active $M = 44.00$, $SD = 11.95$; sham $M = 44.58$, $SD = 14.75$) and were predominantly women (active = 11/13, 84.6%; sham = 8/12, 66.7%). Of these participants, six discontinued treatment prematurely ($n = 4$ active, $n = 2$ sham), and 1 (sham) was lost to follow-up. Reasons for study discontinuation were inability to adhere to the treatment schedule ($n = 3$), medical illness ($n = 2$), and the remaining participants ($n = 2$) did not provide a reason. In addition, one participant (sham) did not complete the DERS at posttreatment due to an administrative error.

Inclusion criteria were age ≥18, principal or co-principal GAD, Clinical Global Impression-Severity rating ≥4, Hamilton Anxiety Rating Scale ≥18, and 17-item Hamilton Rating Scale for Depression ≤17. Participants were excluded for neurological disorder or other serious and/or unstable medical illness or any contraindication for magnetic resonance imaging (MRI, used for rTMS navigation; see Section 2.3) and/or rTMS, current posttraumatic stress disorder, substance use disorder (past 6 months); lifetime bipolar, psychotic, developmental, or obsessive-compulsive disorder; concurrent psychotherapy, or if judged too psychiatrically unstable to participate. Concurrent pharmacotherapy was stabilized prior to study entry (three month stabilization for all but benzodiazepines taken as needed which were stabilized based upon medication half-life).

### 2.2. Measures

Study inclusion criteria were assessed using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998), Clinical Global Impression-Severity scale (Guy, 1976), and structured interview guides for the Hamilton Anxiety Rating Scale (Shear et al., 2001) and 17-item Hamilton Rating Scale for Depression (Williams, 1988). Because improvements in emotion regulation are likely to be associated with a wide range of clinical outcomes (e.g., emotional symptoms, functioning), we chose to include the clinician-rated Clinical Global Impression-Improvement scale (CGI-I, Guy, 1976) as the measure of treatment response. Unlike symptom specific measures (such as the Hamilton Anxiety Rating Scale) the CGI-I rating takes into account improvements in overall emotional symptoms (e.g., anxiety, worry, depression) as well as functional impairment (e.g., decreased avoidance, improved social relationships, improved job performance). The CGI-I rates improvement on a 7-point scale from 1 = *very much improved* to 7 = *very much worse*. Emotion regulation was assessed using the Difficulties in Emotion Regulation Scale (DERS, Gratz & Roemer, 2004) which is a 36-item self-report measure. The six DERS subscales measure: (1) Non-Acceptance: nonacceptance of emotional responses, (2) Goals: difficulties engaging in goal-directed behavior, (3) Impulse Control: impulse control difficulties, (4) Awareness: lack of emotional awareness, (5) Strategies: limited access to emotion regulation strategies, and (6) Clarity: lack of emotional clarity. Higher scores on the DERS indicate more severe difficulties with emotion regulation. Previous research has found the DERS to demonstrate adequate construct validity, good test-retest reliability, and high internal consistency (Gratz & Roemer, 2004).

### 2.3. rTMS

Participants who were randomized to active treatment received 30 daily sessions (5 days/week) of low-frequency rTMS stimulation to the right DLPFC (MNI coordinates: x = 42, y = 36, z = 32) using the NeuroStar TMS Therapy System. Right-side stimulation of the DLPFC was chosen given evidence that emotion regulation processes (e.g., attention and down regulation in response to emotional stimuli) are lateralized to the right side (e.g., Grimm et al., 2008; Leyman, De Raedt, Vanderhasselt, & Baeken, 2009; Van Honk, Schutter, d'Alfonso, Kessels, & de Haan, 2002). Right-sided DLFPC rTMS has also been associated with improvements in anxiety symptoms, including in patients with GAD (e.g., Bystritsky et al., 2008; Mantovani et al., 2007; Watts, Landon, Groft, & Young-Xu, 2012), and may be superior to high-frequency, left-sided stimulation for treating anxiety symptoms (Rossini et al., 2010). Finally, low frequency right-sided stimulation is also better tolerated and may reduce risk of seizure as compared to the high frequency left-sided stimulation. Stimulation parameters (1 Hz, 900 pulses/session, 90% resting motor threshold) were chosen to be the same as those used in a previous open trial of rTMS for GAD (Bystritsky et al., 2008), although the number of sessions was higher in the current study to protect against inadequate dosing. The right DLPFC point for stimulation was identified using structural MRI scan and located using a frameless stereotactic neuronavigation system (see Diefenbach et al., in press for details of neuronavigation procedures). Procedures were similar for those participants receiving sham with the exception that a sham coil (Neuronetics XPLOR coil), which was designed and matched for use in blinded clinical trials, was used.

### 2.4. Procedure

Written informed consent was obtained from study participants prior to entry. Procedures were approved by the Hartford Hospital Institutional Review Board (DIEF003523HI) and the study was listed on clinicaltrials.gov (URL: https://clinicaltrials.gov; Registration Number: NCT01659736). The randomization schedule was developed using a computerized random number generator. Blocked randomization was used with a block size of 10. Participants were randomized to condition at the first treatment session. Study eligibility was determined by a licensed clinical psychologist. The clinical psychologist, who was blind to treatment condition, also completed the CGI-I at posttreatment and 3-month follow-up. The DERS was completed by participants at pretreatment, posttreatment, and 3-month follow-up. The clinician and participants independently completed a self-report measure to assess the blind. At the posttreatment assessment there were no instances of unblinding reported; however, the clinician was able to accurately guess treatment condition for 73.7% of participants (14/19) and 84.2% of participants completing treatment (16/19) accurately guessed treatment condition. In both cases, clinical outcome (i.e., improvement or lack of improvement in symptoms/functioning) was the most common reason given for guesses [reported in 94.7% (18/19) of cases rated the clinician and by 89.5% (17/19) of participants] as opposed to inadequate blinding procedures.

### 2.5. Data analytic plan

#### 2.5.1. Linear mixed effect model

Data distributions of continuous variables were checked for normality using normal probability plots prior to statistical analysis. No transformations were necessary. Descriptive statistics were calculated using all available data at each time point. Outcome analyses were conducted using the intent-to-treat (ITT) sample with a linear mixed effects model with treatment condition (active rTMS vs. sham) as a between-subject factor, time (pretreatment, posttreatment, follow-up) as a within-subject factor and the interaction between treatment condition and time for each outcome. The best-fitting variance-covariance structure for each outcome was selected using Schwartz' Bayesian Information Criterion (BIC). Considered structures were compound symmetry, compound symmetry heterogeneous, autoregressive, autoregressive heterogeneous, random intercept plus autoregressive, unstructured. Least square means and standard errors were plotted for the ITT sample and least square mean comparison post-hoc tests were performed to explain significant effects in the models. Linear contrast of least square mean effect sizes with 95% confidence intervals were computed to illustrate the effect size of group differences in emotion regulation changes over time.

#### 2.5.2. Post-hoc analyses controlling for pretreatment scores

Given results of baseline differences in treatment conditions, post-hoc analyses were conducted on the sample of treatment completers ($n = 9$ participants in active rTMS, $n = 9$ in sham owing to missing DERS data for one participant at posttreatment) to investigate the nature of changes in emotion regulation over time when controlling for pretreatment scores. Percentage of change from (1) pretreatment to posttreatment and (2) pretreatment to follow-up was determined for all measures demonstrating a significant treatment condition by time interaction in linear mixed effects models. Effect size of group differences on the DERS percent of change was determined using Cohen's $d$, and interpreted as 0.20 = small, 0.50 = medium and 0.80 = large (Cohen, 1988). Next, analysis of covariance, controlling for pretreatment scores, was computed comparing the active versus sham treatment completers.

#### 2.5.3. Associations with global treatment response

Lastly, associations between emotion regulation improvements (as measured by percentage change at posttreatment and follow-up) and treatment outcome (as measured by CGI-I) were determined using Spearman's rho correlations (this analysis was used because of small sample size). To ensure that outliers would not bias correlations all variables used in these analyses were checked for outliers (defined as a value falling outside the range of the mean score plus or minus 2.5 standard deviations). Data were checked for the total sample and each treatment condition sample separately, and no outliers were found.

## 3. Results

### 3.1. DERS total score

Least square means for the DERS total score are presented in Table 1 along with treatment condition by time interaction effects and follow-up within group contrasts. As shown in Table 1, there was a statistically significant treatment condition by time interaction, with significant improvements occurring only for those participants receiving active rTMS. The improvement in the active rTMS condition was statistically significant at both posttreatment and follow-up compared to baseline. However, the mean DERS total score was statistically significantly different between the two treatment conditions only at pretreatment [$F(1, 29.2) = 6.26$, $p = 0.02$; partial eta$^2 = 0.249$], with the active rTMS group scoring significantly higher than the sham group. Linear contrast of least square mean effect sizes with 95% confidence intervals of group differences in emotion regulation changes over time are presented in Table 2. These results show large between-group differences in symptom change over time for the total score at both posttreatment and 3-month follow-up. The 95% confidence interval demonstrates a large range, likely owing to the small sample size included in the study.

### 3.2. DERS subscales

Least square means for the DERS subscales are presented in Table 1 along with treatment condition by time interaction effects, and where interaction effects are significant, follow-up within group contrasts. A statistically significant treatment condition by time interaction was found for both the DERS goals and impulse control subscales. In both cases there was a statistically significant improvement in the active rTMS group, but not in the sham group. The improvement in the active rTMS group was statistically significant at both posttreatment and follow-up compared to baseline. However, the treatment conditions differed significantly only at pretreatment [goals $F(1, 31.5) = 12.13$, $p = 0.002$, partial eta$^2 = 0.414$; impulse control $F(1, 28.8) = 7.21$, $p = 0.01$, partial eta$^2 = 0.239$], with the active rTMS group scoring significantly higher than the sham group. There were no statistically significant treatment condition by time interaction effects for the DERS non-acceptance, lack of awareness, emotional clarity, or strategies subscales.

Linear contrast of least square mean effect sizes with 95% confidence intervals of group differences in emotion regulation changes over time are presented in Table 2. These results show the largest between-group difference in symptom change over time for the goals, impulse control, and non-acceptance subscales at posttreatment, and the goals and impulse control subscales at follow-up. The 95% confidence interval demonstrates a large range, likely owing to the small sample size included in the study.

**Table 1**
Least Square Means and Standard Errors for the DERS.

| | Treatment Group | Pretreatment | Posttreatment | Follow-up | Interaction F | Within-Group F |
|---|---|---|---|---|---|---|
| Total | | | | | 4.68* | |
| | Active | 111.31 (6.31)[a] | 90.24 (6.87)[b] | 92.69 (6.87)[b] | | 10.57*** |
| | Sham | 88.50 (6.57) | 87.77 (6.97) | 86.14 (6.98) | | 0.11 |
| Non-Acceptance | | | | | 1.97 | |
| | Active | 19.31 (1.46) | 13.44 (1.68) | 15.55 (1.68) | | NC |
| | Sham | 17.00 (1.52) | 15.64 (1.68) | 15.20 (1.68) | | NC |
| Goals | | | | | 4.20* | |
| | Active | 21.00 (1.36)[a] | 17.52 (1.50)[b] | 17.41 (1.50)[b] | | 5.91** |
| | Sham | 14.67 (1.42) | 15.04 (1.52) | 14.57 (1.52) | | 0.27 |
| Impulse Control | | | | | 5.66** | |
| | Active | 17.54 (1.56)[a] | 12.78 (1.68)[b] | 13.23 (1.68)[b] | | 10.01*** |
| | Sham | 11.50 (1.62) | 11.59 (1.71) | 11.92 (1.71) | | 0.07 |
| Awareness | | | | | 1.53 | |
| | Active | 15.23 (1.21) | 13.53 (1.34) | 14.42 (1.34) | | NC |
| | Sham | 15.25 (1.25) | 15.98 (1.36) | 14.38 (1.36) | | NC |
| Strategies | | | | | 1.22 | |
| | Active | 25.16 (2.11) | 21.96 (2.29) | 21.07 (2.29) | | NC |
| | Sham | 19.42 (2.20) | 18.00 (2.33) | 18.93 (2.33) | | NC |
| Clarity | | | | | 2.27 | |
| | Active | 13.08 (1.16) | 10.37 (1.30) | 10.54 (1.23) | | NC |
| | Sham | 11.17 (1.21) | 11.31 (1.31) | 11.02 (1.27) | | NC |

*Note*. Least square means are shown with standard errors in parentheses. These scores have been adjusted for missing data using a linear mixed effects model. Within-group values with differing superscripts (a versus b) differ significantly. Follow-up within-group comparisons were only completed for measures demonstrating a significant group by time interaction. Active $n = 13$; Sham $n = 12$. NC = not completed. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. dfs for treatment condition by time interaction range = (2, 32.8) to (2, 34.4). dfs for within-group contrasts range = (2, 34.4) to (2, 35.5).

**Table 2**
Between-Group Effect Sizes Comparing the Active and Sham Conditions on Changes in Emotion Regulation Over Time.

| | Endpoint of Change from Baseline | Linear Contrast Effect Size Estimate | 95% Confidence Interval |
|---|---|---|---|
| Total | Post | 20.33 (7.09) | 5.91, 34.75 |
| | Follow-up | 16.26 (7.09) | 1.84, 30.68 |
| Acceptance | Post | 4.51 (2.27) | −0.11, 9.13 |
| | Follow-up | 1.95 (2.27) | −2.66, 6.57 |
| Goals | Post | 4.35 (1.69) | 0.93, 7.78 |
| | Follow-up | 3.99 (1.69) | 0.57, 7.41 |
| Impulse Control | Post | 4.85 (1.66) | 1.48, 8.22 |
| | Follow-up | 4.73 (1.66) | 1.37, 8.11 |
| Awareness | Post | 2.43 (1.59) | −0.80, 5.67 |
| | Follow-up | −0.62 (1.59) | −3.30, 3.16 |
| Strategies | Post | 1.78 (2.31) | −2.90, 6.47 |
| | Follow-up | 3.60 (2.31) | −1.09, 8.28 |
| Clarity | Post | 2.85 (1.58) | −0.34, 6.04 |
| | Follow-up | 2.39 (1.17) | −001, −4.78 |

*Note*. Estimated linear contrast effect size is shown with standard error in parentheses.

### 3.3. Post-hoc analyses controlling for pretreatment scores

Results of post-hoc analysis of covariance (ANCOVA) comparing active versus sham participants on the percentage of change of DERS total score from pre-to-posttreatment while controlling for pretreatment DERS total score indicated a significant effect of treatment condition [$F(1, 17) = 6.62$, $p = 0.021$; partial eta$^2 = 0.306$] with larger change occurring in the active ($M = 0.18$, $SD = 0.15$) than in the sham group ($M = -0.01$, $SD = 0.13$). However, the active ($M = 0.16$, $SD = 0.17$) and sham ($M = 0.03$, $SD = 0.16$) groups no longer differed significantly at 3-month follow-up [$F(1, 17) = 2.62$, $p = 0.126$; partial eta$^2 = 0.149$]. The between-group effect size was large at posttreatment ($d = 1.35$) and moderate to large at 3-month follow-up ($d = 0.78$).

ANCOVA performed on percent change of the DERS impulsivity scale (again controlling for pretreatment scores) indicated larger improvements in the active ($M = 0.29$, $SD = 0.21$) than sham ($M = -0.06$, $SD = 0.21$) groups at posttreatment [$F$ (1, 17) = 8.55, $p = 0.01$; partial eta$^2 = 0.363$]. Significant differences tended to be maintained over the 3-month follow-up [$F$ (1, 17) = 4.56, $p = 0.05$; partial eta$^2 = 0.233$], again with active ($M = 0.25$, SD = 0.20) demonstrating larger changes than sham ($M = -0.06$, SD = 0.30) over time. Between-group effect sizes were large for percentage of change in the DERS impulsivity scale at both posttreatment ($d = 1.67$) and follow-up ($d = 1.21$).

ANCOVA performed on percent change of the DERS goals scale (again controlling for pretreatment scores) indicated no significant differences between active and sham at either posttreatment [Active: $M = 0.16$, $SD = 0.22$; Sham: $M = -0.10$, SD = 0.20; $F$ (1, 17) = 3.07, $p = 0.100$; partial eta$^2 = 0.170$] or 3-month follow-up [Active: $M = 0.16$, $SD = 0.27$; Sham: $M = -0.03$, $SD = 0.25$; $F$ (1, 17) = 1.19, $p = 0.292$; partial eta$^2 = 0.074$]. Between-group effect

sizes were large for percentage of change in the DERS goals scale at posttreatment ($d = 1.24$) and moderate at follow-up ($d = 0.50$).

### 3.4. Associations with global treatment response

Improvements in self-reported emotion regulation difficulties as measured by post-treatment percentage change in the DERS total score were significantly associated with better clinician-rated improvements in global severity and impairment (as measured by the CGI-I, where lower numbers indicate larger improvements) at posttreatment [$r_s(18) = -0.46$, $p = 0.045$] and at 3-month follow-up [$r_s(16) = -0.71$, $p = 0.002$]. When examining the treatment conditions separately, the association remained strong only in the active rTMS condition at posttreatment [posttreatment $r_s(8) = -0.78$, $p = 0.01$; 3-month follow-up $r_s(8) = -0.62$, $p = 0.07$], and not in sham at either timepoint [posttreatment $r_s(8) = 0.41$, $p = 0.27$; 3-month follow-up $r_s(7) = 0.13$, $p = 0.98$].

Improvements in the DERS goals subscale were also associated with global clinical improvements at posttreatment [$r_s(18) = -0.47$, $p = 0.04$], and 3-month follow-up [$r_s(16) = -0.54$, $p = 0.03$]. However, this association held only in the active rTMS treatment condition at posttreatment [active rTMS $r_s(8) = -0.76$, $p = 0.02$; sham $r_s(8) = 0.02$, $p = 0.93$] and not at 3-month follow-up [active rTMS $r_s(8) = -0.36$, $p = 0.34$; sham $r_s(7) = -0.24$, $p = 0.56$]. Improvements in the impulsivity subscale were moderately associated with clinician-rated improvements; however, this correlation did not reach the level of statistical significance [active rTMS $r_s(18) = -0.33$, $p = 0.18$; sham $r_s(16) = -0.29$, $p = 0.27$], thus analyses were not completed separately by treatment condition subgroup.

## 4. Discussion

In a previous study we reported that active rTMS was superior to sham for improving anxiety symptoms (Diefenbach et al., in press). Additional analyses reported here indicate that rTMS of the right DLPFC also improves emotion regulation as measured by the DERS total score in patients with GAD from pre-to-posttreatment and 3-month follow-up, although the two treatment conditions differed significantly on DERS total score only at pre-treatment. Further, analyses indicated that the percentage of improvement in DERS total score was associated with clinician ratings of global clinical outcome. Supplementary analyses indicated that subscales measuring goal-directed behaviors and impulse control demonstrated the largest and statistically significant rTMS treatment effects, although only the goals subscale was associated with clinical outcome. Items on the goals and impulse control subscales largely assess cognitive and behavioral control, respectively. For example, the goals subscale includes items assessing a person's perceived ability to concentrate and mentally focus well enough to continue functioning in spite of feeling distressed. The impulse control subscale is comprised of items assessing the extent to which the person feels emotionally overwhelmed and behaviorally out-of-control when they are distressed.

The DLPFC plays a pivotal role in emotion regulation, specifically with respect to cognitive and behavioral control, by influencing decision-making and flexibly guiding behaviors to meet goals within the situational context (e.g., Morawetz, Bode, Baudewig, Kirilina, & Heekeren, in press). Current results are consistent with previous research in nonclinical samples suggesting that DLPFC neuromodulation alters emotion-related cognitive processes and decision making. For example, anodal left/cathodal right transcranial direct current stimulation (tDCS, parameters which increases left but decrease right DLPFC activation), improves attentional bias for threat (Ironside, O'Shea, Cowen, & Harmer, 2015), whereas the opposite parameters (cathodal left/anodal right, which decreases left but increases right DLPFC activation) are associated with increased rumination in response to interpersonal stress (Kelley, Hortensius, & Harmon-Jones, 2013). In addition decreasing right DLPFC activation improves inhibitory control of emotion during decision making (Cho et al., 2010), while increasing left-sided DLPFC activation enhances intentional efforts to modulate emotional intensity (Feesher, Prehn, Kazzer, Mungee, & Bajbouj, 2014).

The neurobiological mechanism through which DLPFC neuromodulation alters emotion regulation processes is not known. In the current study low frequency stimulation was used to inhibit right DLPFC activity, however, it is important to note this cortical stimulation has an effect on other cortical and subcortical brain regions as well (Siebner, Hartwigsen, Kassuba, & Rothwell, 2009; Tracy et al., 2014). For example, DLPFC neuromodulation alters activation of, and functional connectivity between, the DLPFC and ventromedial prefrontal cortex – a region key to successful emotional inhibition (Baumgartner, Knoch, Hotz, Eisenegger, & Fehr, 2011). In addition, the degree of connectivity between DLPFC and VMPFC is related to treatment outcome of rTMS in a variety of psychiatric conditions (Diefenbach et al., 2015; Fox, Buckner, White, Greicius, & Pascual-Leone, 2012). Left-sided high frequency DLPFC stimulation using rTMS also impacts automatic emotion regulation processes in patients with obsessive-compulsive disorder, perhaps by way of altered frontal-limbic connectivity (de Wit et al., 2015). While these prior studies suggests a possible biological pathway to explain the current results, additional research is needed to determine the neurobiological mechanisms and correlates of improved emotion regulation following rTMS treatment in patients with GAD.

This study is the first to investigate the effect of neuromodulation treatment on emotion regulation in a sample of patients with GAD. Results lend further support to the clinical effects of DLPFC neuromodulation in patients with GAD, although the nature of the relationship between emotion regulation and symptom improvements remains unclear. It is possible that improvements in anxiety symptoms cause improvements in emotion regulation or alternatively that changes in emotion regulation are a mechanism of change for anxiety symptoms. While these findings are encouraging, conclusions should be tempered by study limitations including a small sample. For example, there was a wide range for linear contrast of least square mean effect sizes (a measure of group differences in changes in emotion regulation over time), likely owing to the small sample. Additionally, despite the use of randomization, participants differed on baseline levels of emotion regulation in the two treatment conditions. While significant improvements occurred in the active rTMS treatment condition it is possible that this resulted from regression to the mean. In a post-hoc analysis comparing DERS percentage change while controlling for baseline scores, the DERS total score at posttreatment, and impulsivity scale at posttreatment and follow-up remained statistically significant, suggesting that these findings are perhaps least likely to be attributed to regression to the mean. Additionally, on average, both the active and sham groups continued to demonstrate impaired emotion regulation [defined as a mean score more than two standard deviations above a previously published HC comparison sample (Roemer et al., 2009)], suggesting that although improvements were noted, on average rTMS was not associated with a normalization of emotion regulation in patients with GAD. Nevertheless, it will be important for future research to investigate the efficacy and mechanisms of neuromodulation in larger and better-matched samples of patients with GAD and to determine whether emotion regulation improvements mediate treatment effects of rTMS on clinical symptoms. Lastly, it is a limitation that emotion regulation assessment was conducted using a self-report measure, and it will be important for future research on neuromodulation effects in GAD to include measures of biological (e.g., heart

rate variability) and/or behavioral (e.g., reappraisal task) indices of emotion regulation as well.

## Declaration of conflicts of interest

Drs. Diefenbach and Goethe report that they receive material support from Neuronetics.

Dr. Goethe reports that he has received speaker fees to discuss TMS at professional conferences from Neuronetics and grant support from Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Eisai, Forest, Hoffmann-La Roche, Janssen, Johnson & Johnson, Merck/Schering-Plough, Neuronetics, Neosync, Novartis, Otsuka, Pfizer, Shire Sunovion, Takeda, and Teva. Dr. Tolin receives funding from Palo Alto Health Sciences. Dr. Assaf and Dr. Gueorguieva report no biomedical financial interests or potential conflicts of interest.

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