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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.