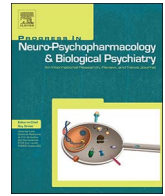


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## Repetitive transcranial magnetic stimulation of the right dorsal lateral prefrontal cortex in the treatment of generalized anxiety disorder: A randomized, double-blind sham controlled clinical trial

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### ABSTRACT

**Background:** Up to 50% of people with GAD fail to respond to first-line pharmacotherapies for generalized anxiety disorder (GAD), partly due to poor treatment compliance rates and partly due to the complex physiology underlying GAD. Thus, new non-invasive techniques, like repetitive transcranial magnetic stimulation (rTMS) are being investigated.

**Methods:** Participants were recruited from two different mood disorder sites: Kingston, Ontario, Canada and Sofia, Bulgaria. Hamilton Anxiety Rating Scale (HARS) scores were reported from patients diagnosed with GAD following treatment with high-frequency (20 Hz) rTMS applied to the right dorsal lateral prefrontal cortex (DLPFC).

**Results:** By the end of 25 rTMS treatments, the ACTIVE (n = 15) treatment group showed a clinically significant reduction in the HARS scores compared to the SHAM (n = 25) group. Hedge's *g* at visit 4 (following 25 rTMS treatments) was 2.1 between ACTIVE and SHAM treatments. Furthermore, at 2 and 4 weeks follow-up (after the end of treatment) HARS scores of the ACTIVE group remained stable and even slightly improved, demonstrating a sustained effect of the response.

**Limitations:** Relatively small sample size of the ACTIVE group as well as the SHAM procedure may limit the generalizability of the results.

**Conclusions:** Thus, participants receiving rTMS treatment showed a clinically significant decrease in reported anxiety symptoms as measured by the HARS. rTMS may be a treatment options for patients treatment refractory to pharmacotherapies.

[www.clinicaltrials.gov](http://www.clinicaltrials.gov): NCT00616447

### 1. Introduction

Globally, anxiety disorders are the most common psychiatric disorders, having a lifetime prevalence of 28% (Kessler et al., 2005). Classified as an anxiety disorder, generalized anxiety disorder (GAD) alone is a chronic and debilitating illness with a 1-year prevalence of approximately 2% (Lieb et al., 2005). Specifically, the symptoms of GAD include chronic extreme and excessive worry (without reason and for at least 6 months) centered on several aspects and activities of one's life and physiological symptoms of arousal (American Psychiatric Association, 1994). GAD is frequently comorbid with other psychiatric conditions, complicating treatment course, remission rates, and con-

tributing to high rates of disability (Wittchen et al., 1994; Stein and Heimberg, 2004).

Early detection and treatment of GAD provides for the best prognoses; however, the longer the symptoms of GAD persist, the more likely the anxiety is to become chronic and the less successful current treatments are in controlling and remitting this illness (Atlamura et al., 2013). Currently, treatment options include psychological therapies and pharmacotherapies (Hoge et al., 2012). First-line drug-treatments for GAD include selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs) and pregabalin (an anticonvulsant); however, up to 50% of people with GAD fail to respond to treatment (Rickels et al., 2006). This has sparked the search

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for other treatment options that has included new pharmacological approaches (e.g., mono- and pharmacotherapies that include mood stabilizers and atypical antipsychotics) as well as application of non-invasive neuromodulation techniques, like repetitive transcranial magnetic stimulation (rTMS). Recently rTMS has been accepted as a safe, effective, and symptom-remitting treatment for some psychiatric illnesses, e.g., Major Depressive Disorder (O'Reardon et al., 2007; Janicak et al., 2010; Janicak et al., 2008; George et al., 2008; Dunner et al., 2014). Preliminary case- and open-label studies using repetitive TMS (rTMS) have shown that this treatment may be anxiolytic in individuals with an anxiety disorder or a disorder comorbid with GAD and thus holds some promise as a potential therapeutic option for people suffering from symptoms of GAD (Bystritsky et al., 2009; Paes et al., 2013; White and Tavakoli, 2015). In an open-label study, Bystritsky et al. (Bystritsky et al., 2009) used six sessions of low-frequency (1 Hz) rTMS over the right dorsal lateral prefrontal cortex (R-DLPFC) to reduce scores on the Hamilton Anxiety Rating Scale by 50% in GAD. In a randomized double-blind placebo controlled clinical trial, Cohen et al. (Cohen et al., 2004) used both low- and high- frequency (1, 10 Hz respectively) rTMS over the R-DLPFC to treat symptoms of post-traumatic stress disorder (PTSD) and concluded that a significant reduction in general anxiety levels was found in favor of the 10 Hz treatment.

Currently, the etiology and pathophysiology of GAD are unknown, complicating the development of novel treatment strategies. Imaging studies point to a hyperactivation of the amygdala, a brain structure typically associated with the modulation of the fear response (Hilbert et al., 2014; Makovac et al., 2015). Hyperactivity in this region may in part be due to neurotransmitter imbalances (Riaza Bermudo-Soriano et al., 2012) that likely leads altered connectivity between the amygdala and prefrontal brain regions and general network dysfunction (Makovac et al., 2015; Tromp et al., 2012; Strawn et al., 2012; Strawn et al., 2013; Roy et al., 2013). While little is currently known about the precise cellular mechanisms by which rTMS produces its effects, there is evidence that it alters cortical excitability that persists after stimulus delivery has ceased (Maeda et al., 2000; Thut and Pascual-Leone, 2010) that then can modulate the network both locally and distally from the stimulation site (Shafi et al., 2012).

Here we investigated high-frequency (20 Hz) rTMS applied to R-DLPFC in a randomized double-blind SHAM controlled clinical trial for 6 weeks (25 rTMS treatments) in patients with GAD. Our results indicate significant sustained clinical improvement in patients' symptoms as classified by the Hamilton Anxiety Rating Scale (HARS).

## 2. Methods

### 2.1. Patients

Participants aged 18 to 65 years old were recruited from two different mood disorder sites: Kingston Ontario, Canada, and Sofia, Bulgaria. Recruitment began in January 2008 and data collection was completed November 2012. Written informed consent was obtained from patients before beginning any study related procedure, in accordance with the Ethics Committee for Multicenter Trials of Ministry of Health (Bulgaria) and Queen's University Research Ethics Board (Canada). A treatment randomization table was generated by a statistician to randomize for treatment order (A: ACTIVE, B; SHAM) and then placed sealed envelopes containing a single allocation (A or B) into a box. Treatment allocation was then performed by an individual who received enrolment logs and enrollment envelopes. Following screening, each participant was instructed to pull the next envelope in the box. This envelop was then given to rTMS administrators. Clinical raters were blinded to the randomization procedure. Clinical raters were blinded to treatment modality and were separate individuals from rTMS administrators. Clinical diagnoses were determined by a psychiatrist using the Diagnostic and Statistical Manual of Mental Disorders, Fourth

Edition (MINI) (American Psychiatric Association, 1994) criteria for primary generalized anxiety disorder (GAD). rTMS administrators were instructed to provide the protocol indicated by letter allocated to the patient: the intensity for both A and B protocols (ACTIVE and SHAM, respectively) remained the same, however, positioning of the coil over the target zone differed (i.e., for SHAM the coil was placed perpendicular to the target region).

Participants without GAD pharmacotherapy for a least two weeks prior to the start of the study or who had 6 weeks of stable pharmacotherapy treatment and/or were enrolled in individual or group supportive psychotherapy were included in this study. Current medication regimes and psychotherapy were followed throughout the treatment. Study exclusion criteria included: a diagnoses of schizophrenia, other psychotic disorders, bipolar I disorder, current major depressive episodes (HDRS (17)  $\geq$  18), or substance and alcohol dependence within the last 6 months; severe axis II disorder; suicidal (score  $\geq$  6, moderate or severe stage in MINI); metallic implant in the cranium (except mouth); severe or unstable medical conditions; ECT treatment within the last three months or have had TMS treatment in the past 6 months; history of epilepsy; neurological disorders leading to increased intracranial pressure; and severe cardiac disorder and/or with intracardiac lines, cardiac pacemakers.

In total, 50 participants were enrolled in the study (10 from the Canadian site and 40 from the Bulgarian site). In total, 25 participants were randomly assigned to the SHAM group and 25 to the ACTIVE group. Of these, 5 participants dropped out immediately following randomization and prior to treatment (from the Bulgarian site); these participants were not included in the analysis. 42 participants completed all 25 rTMS ACTIVE or SHAM treatments. Participants in the ACTIVE group from the Canadian site ( $n = 5$ ) were not included in the analysis as the rTMS stimulation protocol was not correctly applied. The majority of participants were on at least two medications during the duration of the study: Several participants were drug free (ACTIVE:  $n = 6$ ; SHAM:  $n = 11$ ) and the remainder of patients in both SHAM and ACTIVE groups received polypharmacotherapy (two or more concurrent medication). Patients received SSRIs (Paroxetine [ACTIVE: 0; SHAM: 1], Sertraline [ACTIVE: 1; SHAM: 1], Escitalopram [ACTIVE: 3; SHAM: 6]), SNRIs (Venlafaxine [ACTIVE: 3; SHAM: 4], Milnacipran [ACTIVE: 1; SHAM: 1]), SARIs (Trazodone [SHAM: 2]), atypical antidepressants (Mirtazapine [ACTIVE: 1; SHAM: 2]), benzodiazepines (Clonazepam [ACTIVE: 1; SHAM: 1], Lorazepam [SHAM: 1]), non-benzodiazepine hypnotics (Etifoxine [SHAM: 1; ACTIVE: 2], Zolpidem [SHAM: 2], Zopiclone [ACTIVE: 1; SHAM:1]), tricyclic antidepressants (Tianeptine [ACTIVE:1]), typical antipsychotics (Flupentixol [SHAM: 4], Chlorprothixene [SHAM: 1]), atypical antipsychotics (Quetiapine [ACTIVE: 1; SHAM: 1], Amisulpride [ACTIVE: 1], Sulpirid [SHAM:1]), antiparkinsonian anticholinergics (Levodopa [SHAM: 1]), anticonvulsants (Carbamazepine [SHAM: 1], valproic acid [SHAM: 1]), melatonergic antidepressants (Agomelatine [ACTIVE: 1]), and melatonin (ACTIVE: 1; SHAM: 1).

### 2.2. Stimulation parameters

ACTIVE group participants received high frequency ACTIVE rTMS (20 Hz, 110% of the Resting Motor Threshold [RMT], for 20 trains, 9 s per train, 51 s intertrain intervals by figure of 8 shaped coils; Medtronic MagPro R30, Denmark) to the right DLPFC, defined as 5 cm anterior in a parasagittal line to the site of maximal abductor pollicis brevis muscle stimulation: 5 sessions a week for the first 4 weeks; during the 5th week, sessions were reduced to 3 times/week and again to twice a week during the 6th week. SHAM group patients received the coil that was held 90° from the skull, with an intensity of 110% of RMT. The remaining procedure was the same as the ACTIVE group.

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