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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.

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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 contributing 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]), antiparkinsononian anticholinergics (Levocarbidopa [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.

2.3. Outcome measures

The standardized clinical rating scales, Hamilton Anxiety Rating Scale (HARS), Clinical Global Impression Scale (CGI), and the Hamilton Depression Rating Scale (HDRS-21) were used to measure the treatment outcomes.

A total of six visits were required per participant to measure treatment outcomes: The scales were administered and evaluated by a blind rater at the pretreatment baseline phase (visit 1), week 2, 4 and 6 (visit 2, 3, and 4, respectively) and week 8 and 12 (visit 5 and 6, respectively; 2 and 4 weeks following the end of rTMS treatment, respectively).

2.4. Statistical analysis

Analyses were performed using SPSS version 23 (Chicago, IL). Baseline demographic and clinical data to compare SHAM participants recruited from the Kingston and Bulgaria sites and again collapsing sites (ACTIVE and SHAM) were compared using one-way analysis of variance (ANOVA). The effect of TMS treatment on outcome measures was analyzed by comparing treatment (ACTIVE vs SHAM) across visits using a repeated measures ANOVA. A two-way ANOVA (Treatment vs visit) examined main effects and interactions. Missing data was replaced with the last observation carried forward in order to perform intention-to-treat methodology. Independent samples *t*-test and paired *t*-test was used to explore significant interactions. When repeated measures were performed, trend analysis (contrasts) were reported in every case. Neither sphericity of variance nor a significant main effect of the within-subject variable is an assumption of running trend analysis. Hedge's *g* was used to report the effect size (magnitude of the difference) following the 25 treatments (visit 4).

3. Results

3.1. rTMS effects on HARS

Data were collected from the 40 patients; 21 (52%) were male, 19 (48%) were female and ranged from 23 to 57 years old. Table 1 shows baseline demographic and clinical data for ACTIVE and SHAM groups: no significant differences were found for sex, age, HDRS-17, or HARS scores between the two treatment conditions. Participants recruited from the Canadian site (SHAM only) were significantly older (Canada: 47 ± 6 [SD]; Bulgaria: 36 ± 9 [SD]; F [1,23] = 6.55, p = 0.018) and had significantly lower HRDS (Canada: 10 ± 4 [SD]; Bulgaria: 14 ± 2 [SD]) and HARS scores (Canada: 22 ± 3 [SD]; Bulgaria: 31 ± 6 [SD]; F [1,23] = 11.6, p = 0.002; F [1,23] = 12.2, p = 0.002, respectively). It is possible that the Bulgarian participants represented a sicker cohort and may explain any effects of placebo treatment observed in the Canadian participants.

By the end of 25 rTMS treatments, the ACTIVE treatment group showed a clinically significant reduction in HARS scores across the six weeks (4 visits; Fig. 1; 2-way ANOVA revealed a significant within subjects main effect of visit, $F[1, 38] = 144$, $p < 0.001$ and visit x treatment interaction, F [1, 38] = 137, $p < 0.001$; There was also a significant difference between group effect of treatment F [1, 38] = 10.4, p = 0.003). There was no significant decrease in the mean HARS scores for the SHAM group from visit 1 to visit 4 (t [24] = 0.982, p = 0.336). On the first visit (baseline), mean HARS scores of ACTIVE vs SHAM were not significantly different (t [38] = −1.91, p = 0.204). However, by visit 3 (20 treatments) a significant effect of rTMS treatment became evident (t [38] = 5.7, $p < 0.001$) and by visit 4 (25 treatments), the ACTIVE treatment group showed an average 25 (± 4) point reduction on the HARS (scoring from moderate to severe scores at visit 1 [range 25–38] to mild scores by visit 4 [range 3–10]) and was significantly different compared SHAM (t [38] = 8.5, $p < 0.001$; Hedge's g = 2.1; Fig. 1). Clinical response was defined as a ≥ 50% improvement on HARS scores from visit 1 to visit 4: response rate (Bandelow, 2006) was 100% in the ACTIVE group with a mean reduction in HARS scores of 79% (range: 64–92%). HARS scores for the ACTIVE group after visit 4 (25rTMS treatments) ranged from 3 to 10, with 12/15 of the participants scoring in clinically defined 'remission' (< 10 on HARS) (Bandelow, 2006). By study end (visit 6: 12 weeks following the last rTMS treatment), all 15 participants in the ACTIVE group had HARS scores ≤ 8. Mean clinical response to SHAM however, was 8%, with 3 of the 15 SHAM treated participants showing clinical improvement in HARS scores. All three of these participants were recruited from the Kingston site. Furthermore, at 2 and 4 week (visit 5 and 6) follow-up (after the end of rTMS treatment) HARS scores of the ACTIVE group improved further, demonstrating a sustained effect of the response (visit 4 was statistically different from visit 6 in the ACTIVE group: t [14] = 5.06, $p < 0.001$; Fig. 1).

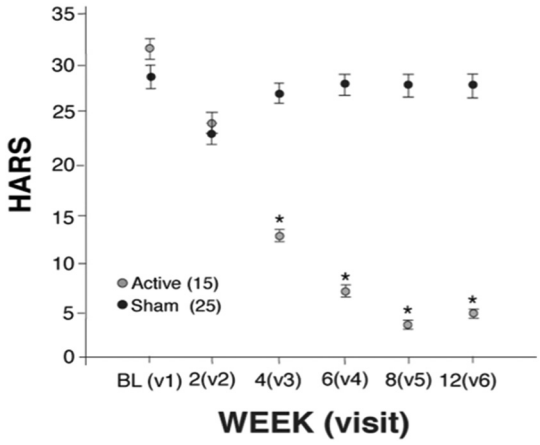

Fig. 1. Hamilton Anxiety Rating Scale (HARS) mean scores (± SE) from baseline (BL; visit[v] 1), weeks 2–6 of treatment (v2–v4) to the follow-up phase, weeks 8 and 12 (v5–6) with a significant difference (*) at week 4(v3), t (38) = 5.74, $p < 0.001$, week 6 (v4), t (38) = 8.50, $p < 0.001$, week 8 (v5), t (38) = 10.8, $p < 0.001$ and week 12 (v6), t (38) = 10.7, $p < 0.001$. Hedge's g at week 6 (v4; between ACTIVE and SHAM) was 2.1.

As shown in Table 2, both the HDRS-21 and CGI mean scores in the ACTIVE group decreased significantly compared to SHAM by the end of rTMS treatment (visit 4; HDRS-21: significant within subject main effect of visit $F[1,38] = 94.8$, $p < 0.001$, significant within subject interaction of visit x treatment $F[1,38] = 120$, $p < 0.001$; and a significant between subject main effect of treatment $F[1,38] = 23.9$, $p < 0.001$. CGI: significant within subject main effect of visit $F[1,38] = 86.8$, $p < 0.001$, a significant within subjects interaction of visit x treatment $F[1,38] = 88.6$, $p < 0.001$; and a significant between subject main effect of treatment $F[1,38] = 6.06$, p = 0.018). Furthermore, scores on both measures remained stable at the four-week follow-up (Table 2). By study end, the rTMS group (ACTIVE) was reporting all normal mood (HDRS-21) and minimal to much improved (CGI) where as SHAM treated participants remained moderately depressed with little reported improvement.

Table 1
Demographic and baseline clinical data for ACTIVE and SHAM treatment groups at baseline (visit 1). Male and female by group was evaluated by Fisher's Exact Test. All other p-values are the result of a one-way ANOVA.

	ACTIVE	SHAM	p-value
Male (%)	9 (22)	12 (30)	p = 0.342
Female (%)	6 (15)	13 (33)	–
Age (years ± SD)	34 ± 7	38 ± 10	p = 0.161
HDRS-17 ± SD	13 ± 3	14 ± 1	p = 0.067
HARS ± SD	29 ± 6	32 ± 5	p = 0.204

Table 2
ANOVA results for HDRS-21and CGI mean (± SD) scores between ACTIVE vs SHAM.

	ACTIVE (mean ± SD)	SHAM (mean ± SD)	ANOVA
HDRS-21			
Baseline (visit 1)	15 ± 1	14 ± 3	$p = 0.065$
Treatment end (visit 4)	4 ± 1	14 ± 6	$p < 0.001$
Six week follow-up (visit 6)	4 ± 1	15 ± 4	$p < 0.001$
CGI			
Baseline (visit 1)	5 ± 1	5 ± 1	$p = 0.451$
Treatment end (visit 4)	3 ± 0.5	5 ± 1	$p < 0.001$
Six week follow-up (visit 6)	2 ± 0.5	5 ± 1	$p < 0.001$

3.2. Adverse events

One participant in the ACTIVE group experience a generalized tonic-clonic seizure during the 20th rTMS treatment. For the duration of the study, this participant (male, age 26) was receiving escitalopram, trazodone, and melatonin; no other significant medical history was noted or use of other substances prior to seizure. The individual fully recovered and continued to finish the study. All patients reported twitching of the facial muscles during RMT determinations. Transient dizziness was also reported in three patients.

4. Discussion

Following 25 treatments with high-frequency (20 Hz) rTMS applied to the right DLPFC, participants receiving the treatment showed a clinically significant decrease in reported anxiety symptoms as measured by the HARS. Before rTMS and despite concurrent pharmacological treatment, participants continued to score in the moderate to extreme range (25–37) of symptomatology on the HARS. Immediately after the full course of rTMS treatment, the scores in the ACTIVE group generally shifted to a mild range (3 − 10). Furthermore, this effect was sustained: at a four-week follow-up visit, participants continued to report fewer anxiety symptoms as the HARS scores continued to significantly decline from those reported at the end of treatment. This study demonstrates that rTMS does have potential as an effective augmentative treatment in GAD.

The findings of this clinical trial of rTMS treatment for symptoms of GAD agree with those of Bystritsky et al. (Bystritsky et al., 2009) who showed that in an open-label study, six sessions of low-frequency (1 Hz) rTMS over the course of three weeks reduced HARS scores in six out of ten participants by 50%; these individuals also scored < 8 on the HARS, meeting criteria for remission. Symptom improvement using rTMS also has been reported in other anxiety disorders such as social anxiety disorder, (Paes et al., 2013) posttraumatic stress disorder, (Berlim and Van den Eynde, 2014) and obsessive compulsive disorder (Gomes et al., 2010; Mantovani et al., 2010; Hawken et al., 2016) To date, this is the first double-blind SHAM-controlled rTMS trial to treat symptoms of GAD.

Furthermore our findings, like those of Bystritsky et al. (Bystritsky et al., 2009) also demonstrated significant improvements in CGI scores. We went on to demonstrate improvements in co-morbid depressive symptoms (HDRS-21 scores) reducing patients' moderate HDRS-21 scores (visit 1, HDRS-21 range: 13–17) to scores in the normal range (visit 4, HDRS: 2–4) following 25 rTMS treatments. TMS seems to successfully ameliorate depressive mood (O'Reardon et al., 2007; Janicak et al., 2010; Janicak et al., 2008; George et al., 2008; Dunner et al., 2014). In an open-label study of 13 patients with co-morbid MDD and GAD, right-sided rTMS at low frequency (1-Hz) followed by treatment with left-sided DLPFC high-frequency (10 Hz), significantly improved both symptoms of depression and GAD (White and Tavakoli, 2015). Here, right-sided high-frequency (20 Hz) to DLPFC had a similar effect. While patients in our study were not majorly depressed, both depressive symptoms and MDD are very often associated with a GAD diagnosis (48% of GAD patients have an ancillary MDD diagnosis (Kessler et al., 2001; Rickels and Rynn, 2002)). A co-morbid incidence of MDD complicates the course and worsens treatment outcomes of GAD symptoms. While the mechanisms and exact neural circuits of depression associated with GAD are unknown, it is reasonable to postulate some overlap in etiology and thus improvement in depressive symptoms may have contributed to the improvement in GAD symptomology. However, the reverse may also be true, as successful drug therapy for GAD has been shown to reduce subsequent episodes of MDD (Davidson et al., 2010). Others argue that MDD and GAD represent two distinct pathologies (Hendriks et al., 2014). Further research is needed to elucidate the pathophysiology of depression co-morbid with other psychiatric diagnoses.

4.1. Limitations

There are a few important limitations to note in the study. Because of the SHAM method used here, it is possible that neither clinical rater nor the patient may have been completely blind to the treatment conditions. Blinding was not assessed in subjects or clinical raters. Because we cannot ensure proper blinding, SHAM individuals may have realized they were not receiving treatment. Therefore, the potential placebo effects may have been mitigated, amplifying the differences between ACTIVE and SHAM HARS scores; however, three of the SHAM-treated participants did show a significant treatment response, from the Kingston site only. In these patients, it is also possible that the SHAM protocol used was biologically active as there is some evidence that tilting the coil relative to the skull may produce some cortical activation (Loo et al., 2000). Furthermore, because there were no ACTIVE participants from the Kingston site, we cannot necessarily generalize our findings gleaned from the Bulgarian ACTIVE group data. It is possible that patients from Canada and Bulgaria represented two different populations, as the Canadian sample was demographically and clinically significantly different than the Bulgarian sample. The relatively small sample size (N = 5) is likely responsible for this difference.

5. Conclusion

Here we demonstrate that high-frequency (20 Hz) rTMS applied to the right DLPFC significantly improves clinical symptoms of GAD. Specifically, 25 rTMS treatments over six weeks produced a clinical response (i.e., reduced HARS scores by > 50%) in all rTMS treated participants, an effect that was sustained for at least four weeks following the end of rTMS treatment. Given the low side-effect profile, future studies should examine drug-naïve patients and also extend the follow-up period beyond one month to determine the duration of clinical efficacy.

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References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorder [DSM-IV], fourth ed. Washington.
Atlamura, A.C., Camuri, G., Dell'Osso, B., 2013. Duration of untreated illness and duration of illness in anxiety disorders: assessment and influence on outcome. Mod. Trends Pharmacopsychiatri. 29, 111–118.
Bandelow, B., 2006. Defining response and remission in anxiety disorders: toward an integrated approach. CNS Spectr. 11, 21–28.

Berlim, M.T., Van den Eynde, F., 2014. Repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex for treating posttraumatic stress disorder: an exploratory meta-analysis of randomized, double-blind and sham-controlled trials. Can. J. Psychiatr. 59, 487–496.
Bystritsky, A., Kermwin, L.E., Feusner, J.D., 2009. A preliminary study of fMRI-guided rTMS in the treatment of generalized anxiety disorder: 6-month follow-up. J. Clin. Psychiatry 70, 431–432.
Cohen, H., Kaplan, Z., Kotler, M., et al., 2004. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in post-traumatic stress disorder: a double-blind, placebo-controlled study. Am. J. Psychiatry 161, 515–524.
Davidson, J.R., Feltner, D.E., Dugar, A., 2010. Management of generalized anxiety disorder in primary care: identifying the challenges and unmet needs. Prim Care Companion J Clin Psychiatry 71, 12.
Dunner, D.L., Aaronson, S.T., Sackeim, H.A., et al., 2014. A multisite, naturalistic, observational study of transcrainial magnetic stimulation for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1-year follow-up period. J. Clin. Psychaitry 75, 1394–1401.
George, M.S., Lisanby, S.H., Avery, D., et al., 2008. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch. Gen. Psychiatry 67, 507–516.
Gomes, P.V.O., Brasil-Neto, J.P., Allam, N., et al., 2010. A randomized, double-blind trial of repetitive transcranial magnetic stimulation in obsessive-compulsive disorder with three-month follow-up. J. Neuropsychiatr. Clin. Neurosci. 24, 437–443.
Hawken, E.R., Dilkov, D., Kaludiev, E., et al., 2016. Transcranial magnetic stimulation of the supplementary motor area in the treatment of obsessive-compulsive disorder: a multi-site study. Int. J. Mol. Sci. 420. http://dx.doi.org/10.3390/ijms17030420.
Hendriks, S.M., Licht, C.M.M., Spijker, J., et al., 2014. Disorder-specific cognitive profiles in major depressive disorder and generalized anxiety disorder. BMC Psychiatry 14, 96. http://dx.doi.org/10.1186/1471-244X-14-96.
Hilbert, K., Lueken, U., Beesdo-Baum, K., 2014. Neural structures, functioning and connectivity in generalized anxiety disorder and interaction with neuroendocrine systems: a systematic review. J. Affect. Disord. 158, 114–126.
Hoge, E.A., Ivkovic, A., Fricchione, G.L., 2012. Generalized anxiety disorder: diagnosis and treatment. BMJ 345, e7500. http://dx.doi.org/10.1136/bmj.e7500.
Janicak, P.G., O'Reardon, J.P., Sampson, S.M., et al., 2008. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. J. Clin. Psychiatry 67, 222–232.
Janicak, P.G., Nahas, Z., Lisanby, S.H., et al., 2010. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month multisite, open-label study. Brain Stimulat. 3, 187–199.
Kessler, R., Keller, M., Hans-Ulrich, W., 2001. The epidemiology of generalized anxiety disorder. Psychiatr. Clin. North. Am. 24, 19–39.
Kessler, R.C., Berglund, P., Demler, O., et al., 2005. Lifetime prevalence and age-of-onset. distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch. Gen. Psychiatry 62, 593–602.
Lieb, R., Becker, E., Altamura, A.C., 2005. The epidemiogy of generalized anxiety disorder. Eur. Neurophyschopharmacol. 15, 445–452.
Loo, C.K., Taylor, J.L., Gandevia, S.C., et al., 2000. Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some “sham” forms active? Biol. Psychiatry 47, 325–331.
Maeda, F., Keenan, J.P., Tormos, J.M., et al., 2000. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin. Neurophysiol. 111, 800–805.
Makovac, E., Meeten, F., Watson, D.R., et al., 2015. Alterations in amygdala-prefrontla functional connectivity account for excessive worry and autonomic dysregulation in generalized anxiety disorder. Biol. Psychiatry. http://dx.doi.org/10.1016/j.biopsych.2015.10.013.
Mantovani, A., Simpson, H.B., Fallon, B.A., et al., 2010. Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. Int. Neuropsychopharmacol. 13, 217–227.
O'Reardon, J.P., Solvason, H.B., Janicak, P.G., et al., 2007. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol. Psychiatry 62, 1208–1216.
Paes, F., Baczynski, T., Novaes, F., et al., 2013. Repetitive transcranial magnetic stimulation (rTMS) to treat social anxiety disorder: case reports and a review of the literature. Clin. Prac. Epidemiol. Men. Health 9, 180–188.
Riaza Bermudo-Soriano, C., Perez-Rodriquez, M.M., Vaquero-Lorenzo, C., et al., 2012. New perspectives in glutamate and anxiety. Pharmacol. Biochem. Behav. 100, 752–774.
Rickels, K., Rynn, M., 2002. Pharmacotherapy of generalized anxiety disorder. J. Clin. Psychiatry 63, 9–16.
Rickels, K., Rynn, M., Iyengar, M., et al., 2006. Remission of generalized anxiety disorder: a review of the paroxetine clinical trials database. J. Clin. Psychiatry 67, 41–47.
Roy, A.K., Fudge, J.L., Kelly, C., et al., 2013. Instrinsic functional connectivity of amygdala-based networks in adolescent generalized anxiety disorder. J. Am. Acad. Child Adolesc. Psychiatry 52, 290–299.
Shafi, M.M., Westover, M.B., Fox, M.D., et al., 2012. Exploration and modulation of brain network interactions with noninvasive brain stimulation in combination with neuroimaging. Eur. J. Neurosci. 35, 805–825.
Stein, M.B., Heimberg, R.G., 2004. Well-being and life satisfaction in generalized anxiety disorder: comparison to major depressive disorder in a community sample. J. Affect. Disord. 79, 161–166.
Strawn, J.R., Bitter, S.M., Weber, W.A., et al., 2012. Neurocircuitry of generalized anxiety disorder in adolescents: a pilot functional neuroimaging and functional connectivity study. Depress Anxiety 29, 939–947.
Strawn, J.R., Wehry, A.M., Chu, W.-J., et al., 2013. Neuroanatomic abnormalities in adolescents with generalized anxiety disorder: a voxel-based morphology study. Depress Anxiety 30, 842–848.
Thut, G., Pascual-Leone, A., 2010. A review of combined TMS-EEG studies to characterize lasting effects of repetitive TMS and assess their usefulness in cognitive and clinical neuroscience. Brain Topogr. 22, 219–232.
Tromp, D.P., Grupe, D.W., Oathes, D.J., et al., 2012. Reduced structural connectivity of a major frontolimbic pathway in generalized anxiety disorder. Arch. Gen. Psychiatry 69, 925–934.
White, D., Tavakoli, S., 2015. Repetitive transcranial magnetic stimulation for treatment of major depressive disorder with comorbid generalized anxiety disorder. Ann. Clin. Psychiatry 27, 192–196.
Wittchen, H.U., Zhao, S., Kessler, R.C., et al., 1994. DSM-III-R generalized anxiety disorder in the national comorbidity survey. Arch. Gen. Psychiatry 51, 355–364.