Non-invasive brain stimulation in generalized anxiety disorder: A systematic review

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ABSTRACT

In the last years, several studies using non-invasive brain stimulation (NIBS) techniques demonstrated that the dorsolateral prefrontal cortex (DLPFC) plays a key role in the neurobiological bases of anxiety disorders. Both transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) applied primarily over the prefrontal cortex have been shown to modulate anxiety symptomatology and attention allocation in the generalized anxiety disorder. A literature search on PubMed and PsycINFO databases following PRISMA guidelines identified 4 TMS studies (one open-label study and three randomized trials with active/sham conditions) and one tDCS case report study that have applied NIBS in patients with GAD. All the studies targeted the DLPFC except one in which the parietal cortex has been stimulated. Overall, the findings would suggest that NIBS could ameliorate anxiety symptoms and that improvements remained stable in the follow-up.

Although a limited number of NIBS studies has been conducted on patients with anxiety disorders, these techniques could represent promising tools for the study of neurofunctional basis of anxiety disorders. Further sham-controlled studies are needed to clarify the mechanisms of action of NIBS in order to optimize stimulation protocols and to verify their effectiveness for treating anxiety symptoms.

1. Introduction

Generalized anxiety disorder (GAD) is one of the most common anxiety disorders (Munir & Hughes, 2017), particularly in women (Ruscio et al., 2017), and consists of unrealistic and persistent worry about everyday things. GAD is associated with considerable functional impairment as individuals can find difficult to control their own fear and worry, and often develop further symptoms including fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbance (American Psychiatric Association, 2013; Bandelow et al., 2017).

Most individuals with diagnosis of GAD have at least one comorbid disorder, typically major depressive disorder (Ruscio et al., 2017). Moreover, comorbidity is particularly high for avoidant and dependent personality disorders (Sanderson et al., 1994).

Although treatment of all anxiety disorders is particularly useful in presence of marked distress or comorbid disorders, they go substantially undertreated (Bandelow et al., 2017). Generally, treatment approach should be chosen considering single patient's characteristics: severity of the disorder, comorbidities, objectives, preferences, previous treatments, personal and community resources (Bandelow et al., 2017). The guidelines of the NICE (National Institute for Health and Care Excellence, 2011) for the treatment of people with GAD with marked functional impairment recommend a drug treatment and an individual high-intensity psychological intervention, such as cognitive behavioral therapy (Strohle et al., 2018).

Currently, etiology of GAD is still not clear. Weems and Silverman (2013) suggested that a number of biological, cognitive, behavioral, and social risk factors are involved in development of anxiety disorders. Some models (Cisler and Koster, 2010) also emphasized the role of attentional biases and information processing/interpretation in etiology and maintenance of anxiety. Attentional biases for threat (ABTs) are frequently observed in clinical (patients with anxiety disorders) and non-clinical (individuals with high anxiety level) populations (for a review, see Cisler and Koster, 2010). These biases have been related to an increase of amygdala activation and a reduced activity of the dorsolateral prefrontal cortex (DLPFC; Bishop et al., 2004).

The prefrontal cortex is considered a key structure for processing and responding to positive and negative emotion-related information. According to the valence-asymmetry hypothesis proposed by Davidson and Irwin (1999), the left and right prefrontal cortices are differently involved in emotion processing, with the right hemisphere mainly involved in negative emotion processing and the left hemisphere engaged in positive emotion processing. The right and the left hemispheres

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might also be differently involved in the development of anxiety and depression. For instance, Heller et al. (1997) proposed that anxious arousal is associated with greater activity in right-hemisphere than in left-hemisphere prefrontal regions, whereas anxious apprehension is associated with greater left-hemisphere activity (see also, Engels et al., 2007). Davidson (1998) proposed a differential involvement of the right and the left prefrontal cortex in anxiety and depression, as a decreased activation in the left prefrontal cortex would be related to depression, whereas an increased activation of the right prefrontal cortex would be specific for anxiety.

A critical contribution to the study of the role of the DLPFC in the genesis of anxiety came from non-invasive brain stimulation (NIBS) studies involving transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).

TMS is a neurostimulation technique based on the principle of electro-magnetic induction of an electric field in the brain allowing focal, non-invasive stimulation of the human cortex. TMS can decrease or increase cortical excitability depending on different parameters (Rossi et al., 2009), such as the intensity of the stimulation (Classen and Stefan, 2008) and the state of excitation of the brain tissue (Parkin et al., 2015). Transcranial direct current stimulation is a non-invasive method of neurostimulation that applies a weak direct current (1–2 mA) between two electrodes placed on the scalp and can modulate cortical excitability, probably changing the resting membrane potential of neurons (Iannone et al., 2016; Miniussi et al., 2008). Generally, this technique might increase or decrease cortical excitability depending on the electrode polarity and current intensity: anodal stimulation might depolarize the neuronal membranes increasing neuronal excitability, whereas cathodal stimulation might lead to neuronal hyperpolarization and inhibition (Nitsche et al., 2008). As for TMS, there is no one-to-one correspondence between the stimulation (with anodal/cathodal electrode) and the excitatory/inhibitory effects because these might be affected by cell morphologies, cortical surface shape or by the interaction between the stimulation sites (Parkin et al., 2015). Therefore, for both techniques the effects of stimulation depend on stimulated brain sites and stimulation parameters (position of the electrodes/coil, size of the electrodes/shape of the coil, stimulation intensity, duration of the stimulation, and the number of sessions) and can only be indirectly inferred by task performance or combining NIBS with other methods (Parkin et al., 2015), such as electroencephalography (EEG) or functional Magnetic Resonance Imaging (fMRI).

TMS and tDCS have been employed in several psychiatric disorders. TMS has been used in clinical contexts with therapeutic purpose for psychiatric (depression, acute mania, bipolar disorders, obsessive-compulsive disorders, schizophrenia, post-traumatic stress disorder, drug craving) and neurologic diseases (Parkinson's disease, tinnitus, spasticity, epilepsy, aphasia), and pain syndromes, such as neuropathic pain, visceral pain or migraine (for the application guidelines of TMS in clinical context and research, see Rossi et al., 2009). Similarly, therapeutic efficacy of tDCS has been tested for the treatment of psychiatric disorders, such as major depression, schizophrenia, and obsessive-compulsive disorder (see Kekic et al., 2016 for a review).

In anxiety disorders, NIBS has been employed with both research and therapeutic purposes mainly stimulating frontal areas. This review article will summarize the current status of research using NIBS in treatment of generalized anxiety disorder. Studies employing TMS or tDCS on GAD patients have been summarized specifying stimulation modalities (brain site, frequency, intensity, and duration of the stimulation and the number of sessions), and reporting the main results and the possible limitations.

2. Methods

2.1. Search strategy

Systematic literature review was conducted following the PRISMA guidelines (Liberati et al., 2009).

A primary search on PubMed and PsycINFO databases until September 2018 has been conducted using the following keywords: "generalized anxiety disorder" or "generalised anxiety disorder" combined with "transcranial stimulation", "TMS", "tDCS", "transcranial magnetic stimulation" or "transcranial direct current stimulation". A further manual search have been conducted on Google Scholar.

2.2. Inclusion criteria

Studies had to meet the following criteria: (1) being full length article published in English in peer-reviewed journals, (2) involving human participants only, (3) reporting original research, (4) using rTMS/tDCS for treatment purposes with detailed description of the stimulation method, (5) including patients with generalized anxiety as the primary diagnosis, and (6) reporting outcome measures about changes in anxiety symptoms.

2.3. Data extraction

Once an article was selected for review, the following data were extracted: authors, inclusion and exclusion criteria, sample characteristics, treatment (NIBS, sessions description), follow-up description, concomitant treatment, study design, symptom measurement, and results. These data were summarized using large tables.

2.4. Study selection

Among the 39 articles from the primary search, 32 articles were excluded for the following reasons: 16 were articles not specifically dealing with NIBS in GAD, 3 did not report data on anxiety symptoms, 12 were review or meta-analysis on NIBS in anxiety or other psychiatry disorders, 1 included animals. Study selection is described in Fig. 1 (PRISMA diagram).

2.5. Quality assessment

The quality of evidence has been classified in high, moderate, low, and very low based on the downgrade factors of the GRADE system (Guyatt et al., 2011). For each study, two independent judges evaluated limitations, inconsistency, indirectness, imprecision and publication bias.

3. Results

Among the 6 included studies (Table 1) investigating the clinical effects of NIBS in patients with GAD, one was an open-label TMS pilot study on 10 patients (Bystritsky et al., 2008), three were randomized, double-blind, sham-controlled TMS studies, including 26 (Diefenbach et al., 2016b), 50 (Dilkov et al., 2017) and 36 (Huang et al., 2018) patients. Moreover, one study (Bystritsky et al., 2009) reported a 6-month follow-up of 3-week TMS treatment reported in a previous article (Bystritsky et al., 2008), and one study (Diefenbach et al., 2016a) reported a secondary analysis from a previous randomized-controlled TMS trial (Diefenbach et al., 2016b). The only selected tDCS study (Shiozawa et al., 2014) was a case report; no sham-controlled tDCS study has been found.

As regards concomitant treatments, in the studies conducted by Bystritsky et al. (2008) and Bystritsky et al. (2009) the participants were allowed to use only stable doses of serotonin reuptake inhibitors or as-needed benzodiazepines if the frequency of use did not exceed 2 times per week; there was no indication of psychotherapy. Dilkov et al. (2017) enrolled participants without pharmacotherapy for at 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. The authors specified the
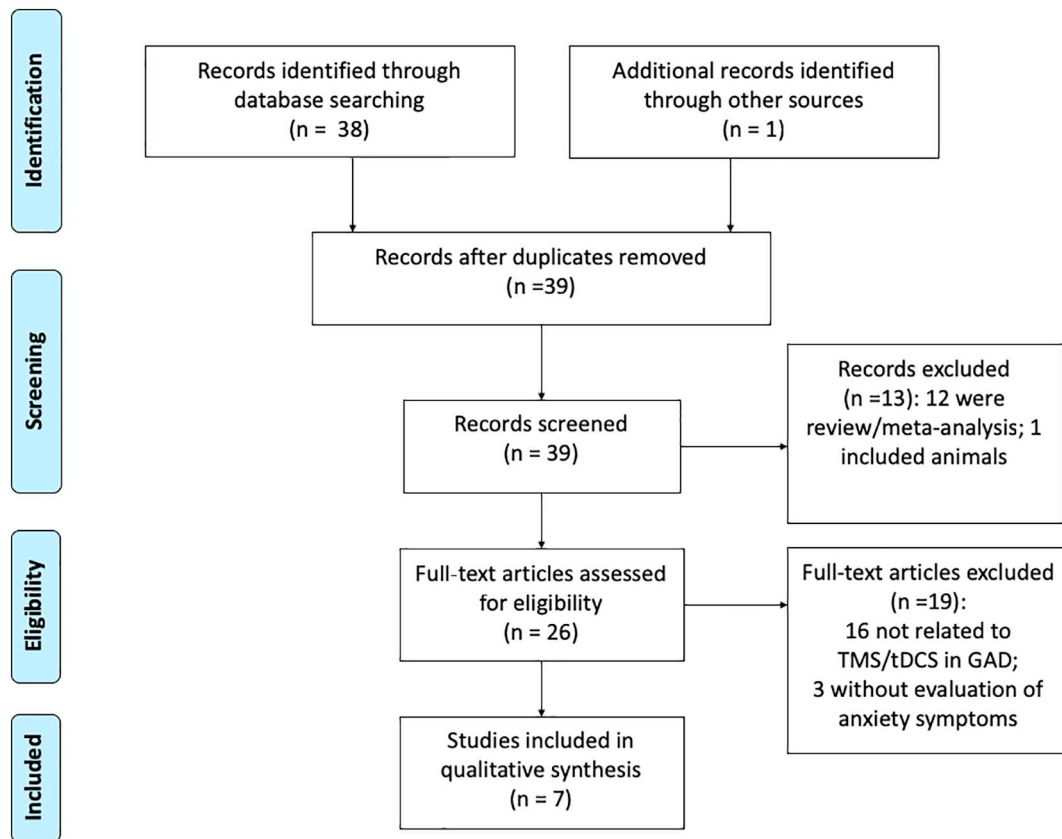
Fig. 1. PRISMA flow diagram of TMS and tDCS selected studies.

pharmacological treatments but did not indicate how many participants underwent psychotherapy and type of psychotherapy. In Diefenbach et al. (2016a) and Diefenbach et al. (2016b) concurrent psychotherapy was considered an exclusion criterion while concurrent pharmacotherapy had to be stabilized for 3 months prior to the trial. Shiozawa et al. (2014) did not specify if the patient was undergoing pharmacological treatment or psychotherapy during the tDCS treatment.

Interestingly, all the studies targeted the prefrontal cortex except Huang et al. (2018) who stimulated the parietal cortex. The number of stimulation sessions varied; one trial (Bystritsky et al., 2008; Bystritsky et al., 2009) delivered 6 sessions in three weeks (two sessions a week). Other studies delivered 5 sessions per week for 2 (Huang et al., 2018), 3 (Shiozawa et al., 2014) or 6 weeks (Diefenbach et al., 2016a; Diefenbach et al., 2016b). Dilkov et al. (2017) delivered 5 sessions a week for the first four weeks, 3 sessions/week during the 5th week, and 2 sessions/week during the 6th week.

Most TMS studies applied a low-frequency stimulation protocol but Dilkov et al. (2017) who used a high frequency (20 Hz) stimulation protocol as in previous studies on different psychiatric populations (Cohen et al., 2004; White and Tavakoli, 2015).

3.1. Quality evaluation

The quality of evidence was judged to be moderate using the GRADE system (Table 1). Four studies started out as high-quality trials due to their design as randomized controlled trials (RCTs), but risk of bias in study design and imprecision lead to downgrade study quality. Based on these limitations, we downgraded 1 study to moderate quality (Huang et al., 2018), 1 study to low quality (Bystritsky et al., 2008), and 2 studies to very low quality (Bystritsky et al., 2009; Shiozawa et al., 2014), while 3 remained high-quality studies (Diefenbach et al., 2016a; Diefenbach et al., 2016b; Dilkov et al., 2017).

3.2. Detailed studies description

Bystritsky et al. (2008) investigated the effects of rTMS for GAD in an open-label paradigm. In their study, 10 participants completed 6 sessions (two sessions a week for 3 weeks) of low-frequency (1 Hz) rTMS over the right DLPFC (localization was guided by fMRI). Low-frequency rTMS (with a putative inhibitory effect) significantly decreased anxiety symptoms associated with GAD as assessed by the Hamilton Rating Scale for Anxiety (HAM-A; Hamilton, 1959) at the end of treatment. This effect was largely maintained at a 6-month follow-up phone interview (Bystritsky et al., 2009) as the symptomatology was reduced with respect to the baseline assessment, although worse than that observed immediately after treatment. This study thus demonstrated the efficacy of fMRI-guided rTMS in individuals with GAD, but this open trial lacked any control condition and its sample size was quite small.

The first double-blind RCT to investigate the efficacy and neural correlates of rTMS in GAD has been conducted by Diefenbach et al. (2016b). In their study, 25 patients were randomly allocated to active rTMS (13 participants) or sham rTMS (12 participants). All participants completed 30 sessions of low frequency (1 Hz) repetitive TMS over the right DLPFC, administered 5 days per week for 6 weeks. Functional data were also acquired while participants performed a gambling task related to uncertainty in a decision-making situation and deemed effective in inducing anxiety. Participants in the active TMS group showed significant improvements of anxiety and depressive symptomatology and increased activation of the right DLPFC during a decision-making gambling task at post-treatment assessment. The reduction of symptomatology resulted stable at 3-month follow-up. Moreover, the changes in neuroactivation after right DLPFC stimulation correlated significantly with changes in worry symptoms (Diefenbach et al., 2016b). The patients were also assessed on emotion regulation via self-report scale reporting an improvement from pre- to post-treatment and 3-

Table 1
Main findings of TMS and tDCS studies in GAD (in chronological order).

Study	Sample	Study type	Groups/ condition	Stimulation protocol	Sessions	Follow-up	Symptoms measures	Main findings	Comments	Quality
Bystritsky et al., 2008	10 patients with GAD with HAM-A ≥ 18	Open-label pilot study	Active TMS only	Low frequency of 1 Hz for 15 min (900 total pulses) at 90% of the resting motor threshold over the DLPFC	6 sessions (two sessions a week for 3 weeks)	6-Month follow-up	HAM-A; HAM-D; FDADS; CGI-S	Significant reduction on HAM-A, HAM-D, and on FDADS; Six participants reached remission.	This was an open trial lacked any control condition and its sample size was quite small	Low
Bystritsky et al., 2009	10 patients with GAD with HAM-A ≥ 18	6-month follow-up of 3-week TMS treatment reported in Bystritsky et al. (2008)	Active TMS only	Low frequency of 1 Hz for 15 min (900 total pulses) at 90% of the resting motor threshold over the DLPFC	6 sessions (two sessions a week for 3 weeks)	6-month follow-up	HAM-A; PGI-I	The clinical status remained improved since baseline and stable compared to the assessment after the treatment		Very low
Shiozawa et al., 2014	1 with diagnosis of GAD	Single-case study	Active tDCS only	2.0 mA for 30 min per day. Cathode was placed over the right DLPFC; anode was placed over the contralateral deltoid.	15 sessions in three weeks	1-month	GADS; BAI; HAM-A	Reduction of anxiety symptoms during 15-day treatment. The effect of tDCS remained stable 1 month after the treatment, when the patient was still asymptomatic	This single-case study conducted on a woman with a pharmaco-resistance GAD have limited generalizability	Very low
Diefenbach et al., 2016b	26 diagnosed with GAD as the principal or coprincipal disorder with CGI-S ≥ 4, HAM-A ≥ 18 HAM-D ≤ 17	Randomized, double-blind, sham-controlled study	Active rTMS (n = 14) and sham (n = 12)	Low frequency of 1 Hz for 15 min (900 total pulses) at 90% of the resting motor threshold over the right DLPFC; Sham treatment: Neuronetics XPLOR coil with ineffective intensity	30 sessions (5 days/ week for 6 weeks; 27,000 total pulses).	After 3 months	HAM-A; HAM-D PSWQ; DASS-DEP;	Improvement on HAM-, HAM-D and DASS-DEP for patients in active group compared to sham group. These findings resulted stable at follow-up.	Limitations regarding the small sample size.	High
Diefenbach et al., 2016a	26 diagnosed with GAD	A secondary analysis from a previous randomized-controlled TMS trial (Diefenbach et al., 2016b)	Active rTMS (n = 14) and sham (n = 12)	Low frequency of 1 Hz for 15 min (900 total pulses) at 90% of the resting motor threshold over the right DLPFC; Sham treatment: Neuronetics XPLOR coil with ineffective intensity	30 sessions (5 days/ week for 6 weeks; 27,000 total pulses).	After 3 months	DERS	Posttreatment and follow-up were statistically different from baseline and sham on DERS	Differences on baseline levels of emotion regulation between of the two groups	Moderate
Dilkov et al., 2017	50 (5 participants dropped out immediately). 42 participants completed all the study	A randomized, double-blind sham controlled clinical study	25 sham group and 25 to the active rTMS group	High frequency rTMS (20 Hz) at 110% of the Resting Motor Threshold, for 20 trains, 9 s per train, with 51 s intertrain intervals delivered by a fig. 8 coil over the right DLPFC. In sham group the coil was held 90° on the skull.	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.	After 2 and 4 weeks following the end of treatment	HAM-A; CGI; HAM-D	The active treatment group showed a clinically significant reduction in HAM-A scores across the six weeks. HAM-D and CGI mean scores in the active group decreased significantly compared to sham by the end of the treatment	One participant in the active group experience a generalized tonic-clonic seizure during the 20th rTMS treatment.	High

Table 1 (*continued*)

Study	Sample	Study type	Groups/condition	Stimulation protocol	Sessions	Follow-up	Symptoms measures	Main findings	Comments	Quality
Huang et al., 2018	36 patients with diagnosis of GAD and insomnia	A randomized, double-blind sham controlled pilot study	18 sham group and 18 to the active TMSgroup	Low frequency -1 Hz at 90% of the resting motor threshold; 3 trains of 500 pulses with an inter-train interval of 10 min, over the right posterior parietal cortex (P4 electrode site). In sham group stimulation was delivered by the 70 mm Double Air Film Sham Coil	10 consecutive days	Two weeks and one month follow-up after the last treatment session	HAM-A; PSQI; HAM-D	Reduction of anxiety levels and improvement of insomnia symptoms. Significantly more responder/remitter participants in the active group compared to sham in post-treatment		Moderate

DLPFC: Dorsolateral prefrontal cortex; HAM-A: Hamilton Rating Scale for Anxiety; HAM-D: Hamilton Rating Scale for Depression; FDADS: Four-Dimensional Anxiety and Depression Scale; CGI–S: Clinical Global Impressions-Severity of Illness; PGI–I: Patient Global Impression of Improvement GADS: Generalized Anxiety Disorder 7-item scale; BAI: Beck Anxiety Inventory; PSWQ: Penn State Worry Questionnaire; DASS-DEP: Depression Anxiety Stress Scales-Depression Subscale; DERS: Difficulties in Emotion Regulation Scale; CGI: Clinical Global Impression Scale.

month follow-up (Diefenbach et al., 2016a). The strength of evidence of this first RCT trial reporting the positive effect of TMS on symptoms of individuals with GAD was mitigated by the relatively small sample size and by differences on baseline levels of emotion regulation between of the two groups of participants.

In line with previous studies employing high-frequency TMS on patients with post- traumatic stress disorder (Cohen et al., 2004) or major depressive disorder with comorbid GAD (White and Tavakoli, 2015), Dilkov et al. (2017) assessed the effect of high frequency (20 Hz) rTMS over the right DLPFC of 50 GAD patients in a randomized double-blind controlled clinical trial. Twenty-five participants were randomly assigned to the control group and 25 to the active treatment group. The treatment consisted of 25 rTMS high-frequency (excitatory) sessions (20 Hz, 110% of the resting motor threshold, for 20 trains, 9 s per train, 51 s intertrain intervals) applied for 6 weeks. The results from this study showed a clinically significant decrease in reported anxiety symptoms as measured by the HAM-A in patients of the active group compared to patients in the sham group. Anxiety levels of participants in the active group remained stable at 2 and 4 weeks after the end of treatment (follow-up), supporting a long lasting effect of TMS. The sham condition in this study, however, was performed holding the coil with only one edge on the scalp oriented at a 90° angle on the skull, so that the coil focus was directed away from participant head. Since patients did not experience any muscular sensations, this procedure might not have ensured an effective blinding of participants for the type of treatment they were receiving.

In a very recent randomized, double-blind sham controlled pilot study, Huang et al. (2018) assessed the effectiveness of a low frequency (1 Hz; 3 trains of 500 pulses with an inter-train interval of 10 min for ten days of treatment) stimulation over the right posterior parietal cortex (P4 electrode site) in reducing both anxiety and insomnia levels in patients with GAD and insomnia. The stimulation site was chosen considering the key role of posterior parietal cortex in mediating interactions between attention and emotion processing (Vossel et al., 2014). The results from this study demonstrated a reduction of anxiety levels and improvement of insomnia symptoms in the active group, with more responder/remitter participants in the active group compared to sham in post-treatment. The results from this study seem to support the positive effect of parietal stimulation, but the mechanisms allowing these effects are not clear, as attentional allocation was not assessed.

Only a single case study (Shiozawa et al., 2014) applied tDCS on a patient with GAD, a 58-year old woman resistant to medical treatment (venlafaxine, sertraline, amitriptiline and quetiapine) who accepted to undergo 10 consecutive sessions of tDCS in three weeks (2.0 mA for 30 min per day). In this stimulation protocol, the cathode was placed over the right DLPFC while the (extracephalic) anode was placed over the contralateral deltoid. Anxiety symptoms were assessed with the Generalized Anxiety Disorder 7-item scale (Spitzer et al., 2006), Beck Anxiety Inventory (Beck and Steer, 1990), and the HAM-A. The results showed a substantial reduction of anxiety symptoms during the 15-day treatment course. The effect of tDCS remained stable 1 month after the treatment, when the patient was still asymptomatic.

4. Discussion

The present review summarized current findings on clinical application of NIBS in GAD. Research on these patients appears to be scarce: only few studies investigating the effects of TMS and only one single case study applying tDCS in patients with GAD fulfilled the inclusion criteria of this review. These studies have led to promising results with a reduction of anxiety symptomatology after the treatment, until 1 month after tDCS (Shiozawa et al., 2014) and 6 months after TMS treatment (Bystritsky et al., 2009).

In most studies, stimulation was delivered over the DLPFC whereas one study targeted the parietal cortex, two regions implied in attention

allocation (Bishop, 2008; Vossel et al., 2014). The DLPFC is also implied in several cognitive processes (e.g., attention and memory), in the interpretation biases, in worry and in ABT. Previous studies on non-clinical samples suggested that it is possible to modify early elaboration of threat by modulating the activity of prefrontal areas, particularly in individuals with high anxiety level (Sagliano et al., 2016; Zwanzger et al., 2014). Vanderhasselt et al. (2011), for example, demonstrated that high-frequency rTMS over the right DLPFC induced attentional biases for threat and that this effect was maximal in participants with the highest state anxiety scores. rTMS has been also used by Balconi and Ferrari (2013) to modulate the activity of the left DLPFC of participants with high or low anxiety (based on the STAI scores). Participants performed a retrieval memory task in which positive and negative emotional word lists had to be encoded and then retrieved among a list of words including new stimuli (distractors) semantically related or unrelated to the old stimuli. The results showed that rTMS affected memory retrieval particularly in high-anxiety participants who showed reduced negative bias and interference effect. Sagliano et al. (2016) found that an online single-pulse TMS over the left DLPFC, with the pulse delivered 100 ms after stimulus onset, determined a disengagement bias in high anxious individuals, while the same stimulation determined an attentional avoidance in low anxious individuals. These studies on non-clinical samples reported that induction of attentional biases by both high frequency TMS over the right DLPFC (Vanderhasselt et al., 2011) and single-pulse TMS over the left DLPFC (Sagliano et al., 2016) is related to levels of anxiety, thus providing convergent findings on the possible application of TMS to modulate ABT in anxious participants.

In the same vein, other studies (e.g., Heeren et al., 2015; Sagliano et al., 2017) applied tDCS in non-clinical samples to assess whether it is possible to modulate levels of anxiety and attentional biases for threat by modifying right or left DLPFC activity, or the balance between them (Davidson, 1998; Sagliano et al., 2017). Clarke et al. (2014) applied anodal tDCS (1 mA for about 17 min) over the left DLPFC in combination with the attention bias modification (ABM; "attend threat" or "avoid threat" attention task) procedure to experimentally confirm the causal role of lateral prefrontal areas in the ABM. The participants who received active anodal tDCS showed greater bias modification compared with participants who underwent the sham stimulation. Heeren et al. (2015) showed that anodal tDCS (2 mA for 25 min) applied over the left DLPFC, combined with ABM, reduced attention allocation on threatening stimuli, whereas ABM alone had no effect on attentional biases. Parallel findings have been reported in a double-blind within-subject study (Heeren et al., 2017) in which anodal tDCS (2 mA for 25 min) over the left DLPFC significantly decreased attentional bias compared to sham stimulation in female individuals with a diagnosis of social anxiety. Sagliano et al. (2017) assessed the effect of bicephalic tDCS (1 mA for 15 min) modulating the balance between right and left DLPFC activity on attentional biases for threat. This study showed that anodal stimulation over the right DLPFC and cathodal stimulation over the left DLPFC determined a disengagement bias in participants with high anxiety level and a facilitation bias in participants with low anxiety level, thus demonstrating the possibility to modulate attentional biases for threat by stimulating DLPFC. Moreover, this study also showed that the specific bias induced by stimulation depended on the anxiety level of the participants. Recently, in a double-blind study, Ironside et al. (2019) applied tDCS (2 mA for 20 min) over the DLPFC in individuals with trait anxiety (score > 45 on the trait measure of STAI) presented with threatening stimuli. The results from this study demonstrated a bilateral reduction of amygdala activity in response to threatening stimuli and a simultaneous increase of activation of cortical regions associated with attentional control (assessed by functional MRI).

Taken together, the studies performed in clinical and non-clinical samples and the evidence reviewed here converge in suggesting a critical role of the DLPFC in anxiety and anxiety-related attentional biases

and in supporting the hypothesis that an unbalanced activity of right and left DLPFC could be responsible for anxiety disorders. Available evidence is also consistent with the idea that NIBS might have therapeutic effects in anxiety disorders. Clinical studies suggest that the stimulation of the right DLPFC by means of both low (Bystritsky et al., 2008; Bystritsky et al., 2009; Diefenbach et al., 2016a; Diefenbach et al., 2016b) and high frequency (Dilkov et al., 2017) TMS or by tDCS (Shiozawa et al., 2014) could reduce patients' anxiety levels. As observed in healthy samples (Ironside et al., 2016), however, a stronger effect might be obtained simultaneously inhibiting the right DLPFC and enhancing the left DLPFC by bicephalic tDCS montages. No study employed bicephalic tDCS for therapeutic purposes in GAD yet, although this seems to be feasible and safe at least in non-clinical samples (Ironside et al., 2016; Sagliano et al., 2017).

In synthesis, the few double-blind randomized trials conducted on GAD would support the research about the clinical application of TMS, whereas evidence about usefulness of tDCS is still limited. The high heterogeneity among available studies in terms of stimulation parameters does not allow proposing empirically based guidelines for maximizing efficacy of these techniques. On the basis of the present findings we could support use of low frequency of 1 Hz TMS for 15 min (900 total pulses; 90% of the resting motor threshold) over the right DLPFC for at least 5 sessions a week for 4 weeks. The present review did not collect sufficient evidence for comparing tDCS protocols, but data from non-clinical samples might suggest using a stimulation protocol at 2.0 mA for 30 min per day with anodal electrode over the left DLPFC and a cathodal electrode over the right DLPFC for at least 5 sessions a week for 4 weeks. Further sham-controlled studies should explore the efficacy of both TMS and tDCS and ascertain the optimal parameter of stimulation (e.g., intensity and duration) and number of sessions. It is worth considering that TMS determines strong, focal effects on the stimulation site so its application can effectively modulate the activity of specific anxiety-related brain areas. Compared to TMS, tDCS is less focal but has several advantages, including low costs and easy management. Therefore, the latter seems better suited for developing double-blind randomized trials aimed at assessing efficacy of NIBS in GAD.

It would be also interesting to evaluate the combined effects of NIBS and pharmacological and/or psychotherapeutic treatments and attentional training. The studies conducted by Clarke et al. (2014) and Heeren et al. (2015) were the first to suggest that tDCS in combination with attentional training may be effective in reducing attentional biases for threat by promoting the attentional allocation on non-threat stimuli. Further studies should test whether combined NIBS and ABM could potentiate the effect of each technique in reducing symptomatology.

As regards psychotherapy, previous studies investigated the effects of the combination of tDCS and cognitive behavioral therapy (CBT) in patients with depression with inconsistent results (Bennabi and Haffen, 2018). Segrave et al. (2014) showed that tDCS coupled with weekly CBT potentiated response to treatment. Donse et al. (2018) also reported that combined rTMS and psychotherapy treatment resulted in 66% response, 56% remission rate at the end of treatment and 60% sustained remission at follow-up in patients with major depressive disorder. In contrast, Brunoni et al. (2014) did not observe relevant effects of a cognitive control training combined with active tDCS compared to sham tDCS. These studies on patients with depression might prompt studies combining NIBS and CBT to verify whether patients with GAD could benefit from combined treatments.

The studies included in this review did not provide sufficient data about the possible interaction between pharmacological treatments and NIBS, as their inclusion criteria implied stabilized pharmacotherapy for a period varying 6 weeks (Dilkov et al., 2017) to 3 months (Diefenbach et al., 2016a). For instance, in Dilkov et al. (2017) the majority of participants took at least two concurrent medications (such as antidepressants, atypical antidepressants, benzodiazepines, hypnotics, tricyclic antidepressants, typical and atypical antipsychotics) during the

study. The effect of combined tDCS and pharmacotherapy has been investigated by Brunoni et al. (2012) who assessed the effectiveness of combined tDCS and sertraline hydrochloride (a SSRI), tDCS-only, sertraline-only and placebo in reducing depressive symptoms in patients with major depressive disorder. Their results showed that tDCS alone and in combination with sertraline had superior antidepressant effects compared to placebo. These findings might encourage future studies about the effect of concomitant pharmacotherapy and NIBS in GAD as well as in patients with depression. Indeed, NIBS, CBT, ABM and pharmacological treatment might operate at different stages (Browning et al., 2010; Crocker et al., 2013). Pharmacological treatment would affect early threat processing and its effectiveness would be related to the involvement of a bottom-up system (Harmer et al., 2006) linked to the amygdala activity. CBT (Goldin et al., 2013), ABM (Browning et al., 2010) and NIBS (Sagliano et al., 2016; Zwanzger et al., 2014) would affect both early and later stages of threat processing and would be mainly related to a top-down system linked to the activity of the DLPFC. Therefore, the application of treatments affecting different systems could lead to more rapid and lasting effects on anxiety symptoms in GAD.

It is also important to consider the relationship between depression and anxiety. In a sample of patients with major depressive disorder with comorbid GAD, White and Tavakoli (2015) employed at low frequency (1-Hz), followed by treatment with rTMS over the left DLPFC at high-frequency (10 Hz) reporting a significant symptoms reduction in most patients, with a percentage of remission of 84.6% for anxiety symptoms and of 76.9% for depressive symptoms. These findings are in line with a previous study reporting a reduction of anxiety symptoms in depressed patients after NIBS (Diefenbach et al., 2013). In the same vein, three of the studies included in this review (Bystritsky et al., 2008; Diefenbach et al., 2016b; Dilkov et al., 2017) reported a significant reduction of depressive symptoms in GAD patients. These results could be interpreted in the light of the model proposed by Davidson (1998) who suggested that the right and the left prefrontal cortices are differentially involved in anxiety and depression, with a decreased activation of left prefrontal cortex in depression, and an increased activation of the right prefrontal cortex in anxiety. This model would foresee that increasing the left DLPFC activity or/and reducing the right DLPFC activity via NIBS might be effective in patients with diagnosis of depression and anxiety.

Two main limitations of this review should be acknowledged. First, we could include only few studies with small sample size and only three double-blind randomized trials. This limited generalizability of the present findings. Moreover, this review could be affected by reporting bias (under-reporting of non-significant results) and publication bias (unpublished studies) that could not be properly addressed here.

Notwithstanding these limitations, and in line with evidence supporting use of NIBS for treatment of psychopathological conditions (Lefaucheur et al., 2014; Lefaucheur et al., 2017) such as social phobia, panic disorder and post-traumatic stress disorder (Iannone et al., 2016; Kar and Sarkar, 2016), obsessive-compulsive disorder (Brunelin et al., 2018), and depression (Liu et al., 2017), the present review would suggest that NIBS could be a promising tool to treat generalized anxiety disorders. The direct modulation of the activity of the brain areas involved in the etiology and maintenance of the disorder by the application of NIBS could be particularly considered for patients with symptoms resistant to other therapies or for those who show adverse side effects with drugs. As anxiety disorders, and particularly GAD, can negatively impact patients' quality of life, and could compromise both emotional and cognitive functioning, identifying effective tools to be implemented in personalised treatment plans is a pressing clinical need. However, the cost/effectiveness ratio of using NIBS in GAD remains to be fully explored.

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