Transcranial Magnetic Stimulation in the Treatment of Anxiety Disorders

13

Giorgio Di Lorenzo, Tommaso B. Jannini, Lucia Longo, Rodolfo Rossi, Alberto Siracusano, and Bernardo Dell'Osso

13.1 Introduction

Anxiety disorders are invalidating conditions, highly prevalent and commonly distributed worldwide [1, 2]. The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) describes anxiety disorders as conditions that feature excessive fear and anxiety responses. Fear can be summarized as a complex series of physiological mechanisms that starts in response to a real or perceived threat (also known as *fight or flight* response), whereas anxiety can be defined as an emotional response to a vague or potential threat [3]; apprehension, sustained

G. Di Lorenzo (✉)
Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

Psychiatry and Clinical Psychology Unit, Fondazione Policlinico Tor Vergata, Rome, Italy

IRCCS Fondazione Santa Lucia, Rome, Italy
e-mail: di.lorenzo@med.uniroma2.it

T. B. Jannini · A. Siracusano
Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

Psychiatry and Clinical Psychology Unit, Fondazione Policlinico Tor Vergata, Rome, Italy

L. Longo · R. Rossi
Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

B. Dell'Osso
Department of Biomedical and Clinical Sciences Luigi Sacco, University of Milan, Milan, Italy

Ospedale Luigi Sacco-Polo Universitario, ASST Fatebenefratelli Sacco, Milan, Italy

Department of Psychiatry and Behavioural Sciences, Bipolar Disorders Clinic, Stanford University, Stanford, CA, USA

CRC "Aldo Ravelli" for Neuro-technology and Experimental Brain Therapeutics, University of Milan, Milan, Italy

B. Dell'Osso, G. Di Lorenzo (eds.), *Non Invasive Brain Stimulation in Psychiatry and Clinical Neurosciences*,
https://doi.org/10.1007/978-3-030-43356-7_13

arousal and vigilance are paired with an autonomic response, leading to specific patterns of defensive behaviour. Anxiety disorders comprise Generalized Anxiety Disorder (GAD), Panic Disorder (PD), Social Anxiety Disorder (SAD), Specific Phobia (SP) and Agoraphobia. Overall, they represent the most common mental disorders in western societies, with a prevalence of 14% of the general population [1]. Nevertheless, anxiety disorders are, unfortunately, under-diagnosed and under-treated. Most anxiety disorders start developing during early ages, with SP and SAD showing a very early onset (7 years) [4, 5]. However, in some anxiety disorders, such as GAD, anxiety can arise in the later years of adulthood [6–8].

Several risk factors are associated with anxiety disorders, including female sex and family history of anxiety or depressive disorders. Furthermore, many stressful life events (such as family divorce, socioeconomical status including poverty and the presence of illness) may be decisive in generating these disorders during childhood [9, 10].

Therapeutic strategies for managing acute anxiety symptoms (mainly benzodiazepines) and the whole anxiety syndrome (with psychopharmacological therapy, mainly drugs modulating serotonin transmission, and/or psychotherapy, mainly cognitive behavioral therapy) are frequently effective. Increasingly specific treatments for anxiety disorders are necessary not only to increase the efficacy and the effectiveness but also, if not above all, for better management of the side effects of the drugs, in particular in special populations (e.g., childhood and adolescence, women in peripartum period, the elderly people) and in those patients with comorbid conditions for other psychiatric and medical diseases. Non-invasive brain stimulation (NIBS) techniques provide an alternative treatment, directed at the stimulation and modulation of the activity of a specific brain area implicated in the circuity sustaining anxiety. In this chapter, after a brief overview of the main cortical neural circuits implicated in anxiety disorders, we will present the state of the art of the clinical use of Transcranial Magnetic Stimulation (TMS) protocols[1] in the treatment of anxiety disorders, through the description (and the summary in the Table 13.1) of the main findings of studies in which TMS was used to treat the different types of anxiety disorders.

13.2 Cortical Neural Circuits in the Pathophysiology of Anxiety

The central neural mechanisms underlying fear and anxiety share many common features, although the exact cortical neural circuitries of anxiety are still to be elucidated. Recent studies have highlighted what could be called an “anxiety network”, i.e. a complex system of brain structures that are mutually co-activated during anxiety processes [11] (see Fig. 13.1). An important role in

[1] See Chap. 1 for details about the general technical bases of TMS and its several therapeutic protocols.

Table 13.1 Main descriptive, technical and clinical features of the studies in which TMS was used as a treatment for anxiety disorders

Authors	Year	Disorder	Study type	N	M/F	Psychiatric comorbidities	Drug therapy	Stimulation site	Stimulation site identification	TMS coil	Stimulation type	Frequency/ Intensity	Pulses per session	Session number and duration	Main outcomes (changes in)	Main findings
Notzon et al.	2015	SP (spiders)	RCT	81	9/72	No	No	Left DLPFC	No	8-figure	iTBS	15 Hz/80% RMT	600	1 × 3′	SPQ, FSQ, ASI	No symptom changes
Herrman et al.	2017	SP (heights)	RCT	39	13/26	No	No	vmPFC	Fpz	8-figure	aHF rTMS	10 Hz/100% RMT	1560	2 × 20′	AQ, BAT	Symptom improvement
Paes et al.	2013	SAD	CS	1	1/0	No	No	Right vmPFC	No	8-figure	LF rTMS	1 Hz/120% MT	1500	1 × 25′	SSI, BDI, BAI	Symptom improvement
Paes et al.	2013	SAD	SSD	2	1/1	MDD	SSRI	Right vmPFC	No	8-figure	LF rTMS	1 Hz/120% MT	1500	12 × 25′	LSAS, BDI, BAI	Symptom improvement
Zwanzger et al.	2002	PD	CS	1	0/1	No	No	Right DLPFC	No	8-figure	LF rTMS	1 Hz/110% MT	1200	10 × N.A.	ACI, PSS, HAS, PAS	Symptom improvement
Guaiana et al.	2005	PD	CS	1	0/1	No	No	Right and left PFC	No	8-figure	LF and HF rTMS	1 Hz/100% MT 20 Hz/100% MT	600	9 × N.A. 20 × N.A.	PDSS	Symptom improvement only after HF rTMS
Dresler et al.	2009	PD	CS	1	1/0	MDD	TCA	Left DLPFC	No	8-figure	HF rTMS	10 Hz/110% MT	2400	15 × 20′	HDS, Stroop accuracy	No changes in task performance
Machado et al.	2014	PD	CS	1	0/1	No	No	Right and left DLPFC	No	8-figure	LF and HF rTMS	1 Hz/120% MT 10 Hz/120 MT	1000 (right)/ N.A. (left)	12 × 15′	BAI, PDSS	Symptom improvement
Mantovani et al.	2007	PD	OLT	6	3/3	MDD	SSRI, NaSSA, BZD, AED	Right DLPFC	No	8-figure	LF rTMS	1 Hz/100% RMT	1200	10 × 28′	PDSS, SCRAS, HAS	Symptom improvement
Prasko et al.	2007	PD	RCT	15	4/11	No	SSRI	Right DLPFC	No	8-figure	LF rTMS	1 Hz/110% MT	1800	10 × 30′	PDSS, BAI, HAMA	Symptom improvement

(continued)

Table 13.1 (continued)

Authors	Year	Disorder	Study type	N	M/F	Psychiatric comorbidities	Drug therapy	Stimulation site	Stimulation site identification	TMS coil	Stimulation type	Frequency/ Intensity	Pulses per session	Session number and duration	Main outcomes (changes in)	Main findings
Mantovani et al.	2013	PD	RCT	25	12/13	MDD	SSRI, SNRI, NaSSA, BZD, AED, AAP, SARI, LDX, Li	Right DLPFC	No	8-figure	LF rTMS	1 Hz/110% RMT	1800	40 × 30′	PDSS, HDRS	Symptom improvement
Kumar et al.	2018	PD	OLT	13	NS	MDD	Yes (N.A.)	Left DLPFC	No	8-figure	HF rTMS	20 Hz/110% RMT	1000	20 × 4′	PDSS, HDRS	Symptom improvement
Bystritsky et al.	2008	GAD	OLT	10	5/5	No	SSRI, BZD	Right DLPFC	MRI-guided	8-figure	LF rTMS	1 Hz/90% RMT	900	6 × 15′	HAM-A, CGI-I	Symptom improvement
White et al.	2015	GAD	OLT	13	5/8	MDD	No	Right and left DLPFC	No	8-figure	LF and HF rTMS	1 Hz/N.A. 10 Hz/N.A.	1000	24–36 × N.A.	GAD-7, HDRS-21	Symptom improvement
Diefenbach et al.	2016	GAD	RCT	25	6/19	No	Yes (N.A.)	Right DLPFC	MRI-guided	8-figure	LF rTMS	1 Hz/90 RMT	900	30 × 15′	HRS-A	Symptom improvement
Dilkov et al.	2017	GAD	RCT	40	21/19	No	SSRI, SNRI, SARI, NaSSA, BZD, NBZD, APD, AAP, APK, AED	Right DLPFC	No	8-figure	HF rTMS	20 Hz/110 RMT	1600	25 × 20′	HRS-A, CGI-I	Symptom improvement

Assaf et al.	2018	GAD	RCT	16	7/24	No	Yes (N.A.)	Right DLPFC	MRI-guided	8-figure	LF rTMS	1 Hz/90% RMT	900	30 × 15′	PSWQ	Symptom improvement
Huang et al.	2018	GAD	RCT	36	18/18	Insomnia	SSRI, BZD	Right PC	No	8-figure	LF rTMS	1 Hz/90% RMT	1500	10 × 36′	HRS-A	Symptom improvement
Depper-mann et al.	2017	AGO	RCT	44	17/27	PD, depres-sion	Yes (N.A.)	Left DLPFC	No	8-figure	iTBS	15 Hz/80% RMT	600	15 × 3′	PAS, HAMA, CAQ, ES-fNIRS	No verum iTBS effect on symptoms; Verum iTBS increased bilateral PFC activity

AAP atypical antipsychotic, *AED* antiepileptic drugs, *AGO* agoraphobia, *APD* antipsychotic drugs, *APK* antiparkinsonian drugs, *AQ* acrophobia questionnaire, *ASI* anxiety sensitivity index, *BAI* Beck Anxiety Inventory, *BAT* behavioral avoidance test, *BDI* Beck Depression Inventory, *BZD* benzodiazepines, *CAQ* cardiac anxiety questionnaire, *CGI-I* clinical global impression—improvement scale, *CS* case study, *DLPFC* dorsolateral prefrontal cortex, *ES-fNIRS* emotional stroop test during recordings of functional near infrareds spectroscopy, *FSQ* fear of spiders questionnaire, *HAMA* Hamilton rating scale for anxiety, *HAS* Hamilton anxiety scale, *HDRS* Hamilton depression rating scale, *HDS* Hamilton depression scale, *HF* high frequency, *iTBS* intermittent theta-burst stimulation, *LDX* lisdexamfetamine, *LF* low frequency, *Li* lithium, *LSAS* Liebowitz social anxiety scale, *MDD* major depressive disorder, *MRI* magnetic resonance imaging, *N.A.* not applicable, *NaSSA* noradrenergic and specific serotoninergic antidepressant, *NBDZ* nonbenzodiazepine drugs, *OLT* open label trial, *PAS* panic and agoraphobia scale, *PFC* prefrontal cortex, *PC* parietal cortex, *PD* panic disorder, *PDSS* panic disorder severity scale, *PSS* panic symptom scale, *PSWQ* Penn State Worry Questionnaire, *RMT* resting motor threshold, *rTMS* repetitive transcranial magnetic stimulation, *SAD* social anxiety disorder, *SARI* serotonin agonist and reuptake inhibitor, *SCRAS* Sheehan clinician rated anxiety scale, *SNRI* serotonin noradrenalin reuptake inhibitor, *SP* specific phobia, *SPQ* spider phobia questionnaire, *SSD* single subject design, *SSI* social skill inventory, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant, *vmPFC* ventromedial prefrontal cortex

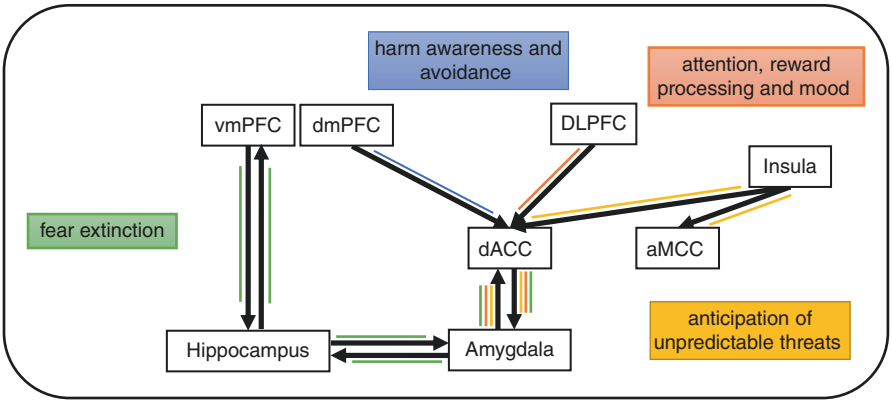

Fig. 13.1 A schematic representation of main brain structures involved in the so-called "anxiety network". *aMCC* anterior midcingulate cortex, *dACC* dorsal anterior cingulate cortex, *DLPFC* dorsolateral prefrontal cortex, *dmPFC* dorsomedial prefrontal cortex, *vmPFC* ventromedial prefrontal cortex

this network is played by the prefrontal cortex (PFC), which deeply interacts with the dorsal anterior cingulate cortex (dACC). Based on functional magnetic resonance imaging (fMRI) studies, the complex dorsomedial PFC (dmPFC)/dACC shows elevated activity in most anxiety disorders, reflecting its fundamental function of harm awareness and avoidance [12]. Moreover, the limbic system seems to be deeply implicated in the pathogenesis of anxiety. Besides dACC, in fact, the subgenual anterior cingulate cortex (sgACC), situated under the *genu* of the *corpus callosum*, plays a key role in processing autonomic responses to emotional stimuli (visceral feedback), such as fear or stress [13]. Indeed, Jaworska and colleagues found an inverse relation between sgACC volumes and anxiety symptoms, highlighting its role in the pathophysiology of anxiety and mood disorders [14].

Other important pathological alterations associated with anxiety include the hypoactivity of the left dorsolateral prefrontal cortex (left DLPFC) and the hyperactivity of the right DLPFC, both observed in patients with PD [15–17]. The DLPFC shows intimate connections with several structures of the meso-cortico-limbic reward circuit, e.g. the ACC, typically associated with attention, reward processing and mood, and the amygdala [18]. Amygdala, a cluster of nuclei deeply implicated in fear generalization [19], seems to work together with the aforementioned complex dmPFC/dACC in the pathophysiology of anxiety. This connectivity, in fact, is straightened when individuals with higher dispositional anxiety are exposed to the threat of unpredictable shock [20].

Failure and delay in fear extinction are intensely implicated in anxiety disorders. The process of constructing new memories involves the extinction of the old ones and, thus, the inhibition of original condition trace that may lead to a dysfunctional state [21]. To this regard, the hippocampus seems to work together with the amygdala in fear extinction, being activated jointly with the vmPFC [22, 23].

Furthermore, also the insula and the bed nucleus of the stria terminalis (BNST) are commonly implicated in the generation of anxiety in humans. Both are broadly

involved in the anticipation of unpredictable threats, being heightened either in post-traumatic stress disorder (PTSD) or in PD [24, 25]. In particular, functional neuroimaging studies showed that the anterior insular cortex may be vastly involved in the anticipation of unpredictable aversive events (e.g. stimuli given with a temporal unpredictability, occurring at any time) [26, 27]. As many of these anxiety-related structures seem to work in concert with other regions of the brain, the anterior insula shows intrinsic connections with the anterior midcingulate cortex (aMCC) and the dACC. This complex is thought to be part of the so-called salience network, a brain system involved in the detection of behaviourally relevant stimuli and the coordination of adaptive responses [28–30].

13.3 TMS in the Treatment of Specific Phobias

Specific phobias (SPs) represent anxiety disorders in which fear, anxiety and avoidance are elicited by a particular situation or object (i.e. heights, spiders, etc.) [31].

To date, in the literature, only two studies that use repetitive TMS (rTMS) in SP patients are available. Although preliminary, these results show that excitatory TMS sessions on PFC have some beneficial effects on patients. Nevertheless, an important heterogeneity in terms of the protocol used, specific cortical targets and symptoms can be observed in these studies. This does not allow drawing any specific conclusion yet, but, on the other hand, it could pave the way for future and more standardized trials.

The first TMS study on patients with SP used virtual reality scenarios and was conducted on 41 participants with spider phobia versus 40 healthy adult controls [16]. Authors used several measurements to assess symptoms, such as the Specific Phobia Questionnaire (SPQ) [32] and the Fear of Spiders Questionnaire (FSQ) [33]. Anxiety and disgust were considered as well through the Questionnaire for the Assessment of Disgust Sensitivity [34], the Subjective Units of Discomfort Scale [35] and the Anxiety Sensitivity Index [36]. Autonomic responses were recorded by monitoring the heart rate (HR) and skin conductance. The protocol consisted of one session of intermittent Theta Burst Stimulation (iTBS) over the left DLPFC. Authors found that iTBS did not impact on self-report measures, but only on heart rate variability, a marker of mental well-being [37], increasing its levels in the active group. No difference was reported in the sham group.

On the other hand, Herrmann et al. used rTMS over the vmPFC on acrophobic patients [38]. This protocol consisted of two sessions of 10 Hz rTMS conducted on 20 participants and 19 controls (average age 44.9, standard deviation 13.1), followed by virtual reality exposure therapy (VRET). Results on self-reported measurements showed that high-frequency rTMS improved the VRET response of acrophobia symptoms, providing the first proof of concept of its efficacy in specific phobias.

13.4 TMS in the Treatment of Social Anxiety Disorder

Social anxiety disorder (SAD) is a common and debilitating condition that features fear of scrutiny by other people and avoidance of social situations, associated with high vegetative responses [31]. The application of rTMS in people with SAD is now preliminary and at early stages. The lack of standardized, double-blinded, sham-controlled protocols has led to inconclusive results about the efficacy of this treatment. However, results from the only two trials conducted so far using low-frequency stimulation seem to be encouraging.

The first study that used rTMS to treat SAD was a case report done by Paes et al. on a 38-year-old male patient [39]. This patient received a single session of 1 Hz (low frequency) rTMS applied over the right vmPFC. Symptoms were evaluated using the Beck Anxiety Inventory (BAI) and the Social Skills Inventory (SSI) [40, 41]. Scores on BAI and symptoms were significantly decreased compared to pre-TMS treatment and, after 2 months, the patient showed only a mild increase of anxiety. The same authors extended their clinical trial to 2 additional patients: a 23-year-old male and a 45-year-old female [42]. Both were diagnosed with SAD and comorbid depression. They were treated with a similar protocol to that in a previous study, using low-frequency rTMS (1 Hz) over the right vmPFC, 3 times per week, for 4 weeks (12 stimulations in total). Anxiety symptoms were evaluated using BAI and Liebowitz Social Anxiety Scale (LSAS) [43] at baseline, 2 and 4 weeks of TMS and after 2 weeks of follow-up. Both patients showed a significant decrease of BAI and LSAS scores, maintaining the same trend at the follow-up examination. These improvements were also observed for depressive symptoms, assessed with the Beck Depression Inventory [44].

13.5 TMS in the Treatment of Panic Disorder

Panic disorder (PD) is described in DSM-5 as a condition in which patients experience recurrent and unexpected panic attacks followed by anticipatory anxiety and phobic avoidance. A panic attack is characterized by intense fear or discomfort associated with a powerful vegetative response that reaches the peak in a very short time [31].

Most studies with rTMS in patients with PD—eight, taken as a whole—were found to be single case reports, providing a wide range of clinical scenarios. In particular, only two randomized, double-blind, sham-controlled studies are available in the literature, whereas the remaining ones are open-label reports. Even though these data have to be considered as preliminary, the results of single case studies seem to be consistent with those from more standardized protocols, supporting the effectiveness of rTMS in the treatment of PD. However, more trials with a sufficient number of stimulating sessions and larger samples are required to make consistent conclusions.

The first trial was a single case study conducted on a 52-year-old woman who had been suffering from PD with six panic attacks per week for 13 months [45]. This patient was treated with low-frequency rTMS (1 Hz) over the right DLPFC for 2 weeks. Symptoms were assessed using the Panic and Agoraphobia Scale (PAS) [46], the Hamilton Anxiety Scale (HAS) [47] and by determining cortisol and

adrenocorticotropic hormone (ACTH) blood levels during a cholecystokinin (CCK)-4 challenge. After 2 weeks of treatment, the patient scored significantly better both on PAS and on HAS. Moreover, a marked reduction in her cortisol levels during CCK-4 challenge was observed.

Guaiana and colleagues treated a 34-year-old female with 9 sessions of low-frequency rTMS (1 Hz) over the right PFC, without observing any clinically relevant result. However, after switching to 20 sessions of a high-frequency protocol (20 Hz) over the left PFC, a significant improvement in PD symptoms was observed [48].

Dresler and co-workers conducted a single case study on a 44-year-old man who was suffering from PD and comorbid depression [49]. The patient was treated with a high-frequency rTMS (10 Hz) over the left DLPFC, once a day, five times per week over 3 weeks. A Stroop task, involving 12-panic-related and 12 neutral words displayed on a screen in three different colours, was presented to test the therapeutic effect. Although rTMS did not impact on the Stroop task, the authors reported no further panic attack that occurred during the treatment.

The last single case study was conducted by Machado et al. on a 34-year-old patient, refractory to cognitive behaviour therapy [50]. The protocol consisted of a sequential stimulation of the right DLPFC (1 Hz) and left DLPFC (10 Hz), 3 times per week for 4 weeks, resulting in a significant improvement of PD symptoms assessed with BAI and Panic Disorder Severity Scale (PDSS).

Mantovani and co-authors assessed rTMS treatment in six patients with PD and comorbid depression, using a protocol of 1 Hz stimulation over the right DLPFC for 2 weeks in an open-label trial [51]. Patients scored significantly better than baseline in the Sheehan Clinician Rated Anxiety Scale (SCRAS) [52], the HAS and the Hamilton Depression Scale (HDS) in the first and the second week of treatment. The same authors conducted a randomized, double-blinded, sham-controlled clinical trial extending the same clinical population up to 25 patients [53]. The treatment consisted of low-frequency stimulation (1 Hz) over the right DLPFC, once a day for 5 consecutive days, for 4 weeks. With regard to panic symptoms, half of the participants from the active group demonstrated a full response of the treatment, whereas in the sham group, the percentage of responders was only 8%.

Prasko et al. recruited 15 patients suffering from PD and resistant to selective serotonin reuptake inhibitor (SSRI) therapy and randomly assigned them to either active treatment with 10 sessions of 1 Hz rTMS over the right DLPFC or the sham group [54]. In both cases, the patients were taking SSRI therapy. The aim was to compare the efficacy at the second and fourth week. The results showed that treatment effect did not differ between groups, since both of them improved during the study period. This negative finding, as suggested by the authors, could be due to small sample size.

The last study was performed by Kumar et al. on 13 drug-resistant patients who were suffering from PD in comorbidity with a major depressive disorder (MDD) [55]. The protocol was structured as 20 sessions of 20 Hz (high frequency) rTMS over the left DLPFC, 5 days per week, over a period of 4 weeks. The symptoms were assessed via PDSS and HDS, showing a significant reduction of scores in both scales.

13.6 TMS as Treatment of Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is a prevalent condition affecting the 2.9% of the adult population in the U.S. Patients with GAD experience excessive anxiety and feeling of apprehensive expectation, being unable to control the worry. This clinical picture is often associated with restlessness, irritably, muscle tension, sleep disturbance and somatization [31].

The application of rTMS in patients diagnosed with GAD seems to be one of the more promising NIBS treatment among the various anxiety disorders. Four randomized, sham-controlled, double-blinded clinical trials have shown positive outcomes in treating this condition, with low-frequency stimulation over the right DLPFC being the most used protocol. However, the sample sizes of these trials (13–36 patients) allow to draw only some preliminary conclusions. This means that future studies with larger populations will be required to draw more consistent conclusions.

Bystrisky and colleagues were the first to use rTMS to treat GAD, stimulating ten participants over the right DLPFC with 1 Hz (low frequency) [56]. They completed 6 sessions over a period of 3 weeks. Patients first underwent an fMRI task to identify the most active location of the prefrontal cortex. The symptoms were monitored using HAM-A [47] and CGI-I, defining the treatment response as a ≥50% score reduction of these scales. Overall, rTMS was associated with a significant decrease of both HAM-A and CGI-I in 6 participants (60%).

Another open-label trial was conducted by White and Tavakoli on 13 patients with GAD and comorbid MDD [57]. The protocol they used consisted of the application of low-frequency rTMS (1 Hz) over the right DLPFC followed by a high-frequency rTMS (10 Hz) over the left DLPFC. The number of stimulations ranged from 24 to 36 over 5 to 6 weeks. At the end of the treatment period, 11 out of 13 patients (84.6%) reported symptom remission, scoring less than 5 on the GAD Scale (GAD-7) [58], and 10 out of 13 patients (79.9%) did the same on the Hamilton Rating Scale for Depression (HAM-D-21), scoring less than 8.

The first randomized, double-blind, sham-controlled clinical trial was performed by Diefenbach et al. on 25 patients (13 active vs. 12 sham) diagnosed with GAD [59]. The active group was treated using a low-frequency rTMS delivered over the right DLPFC for 15 min, for 30 sessions (5 days/week for 6 weeks). Patients were also asked to undergo a decision gambling task with fMRI to localize the area to stimulate. Symptoms were assessed via HARS and the Penn State Worry Questionnaire (PSWQ) [60]. At post-treatment, significantly more patients met the responder and the remitter status in the active versus sham group, showing this trend even at 3-month follow-up. The same authors published additional material on the same cohort of patients, showing that patients treated with rTMS had significant improvements in self-reported emotion regulation difficulties at 3-month follow up [61].

Dilikov et al. recruited 40 patients with GAD, randomly assigning them to active [15] and sham groups [25, 62]. Authors used high-frequency-stimulation (20 Hz) rTMS applied over the right DLPFC. The active group received 5 sessions per week for the first 4 weeks. During the fifth week, the sessions were reduced to 3 times per week, whereas at the sixth and final week, the patients received 2 sessions of rTMS. The symptoms were evaluated using the HARS. By the end of 25 rTMS treatments, the patients in the active group scored significantly less

compared to those in the sham group. Moreover, HARS scores remained stable at the 4-week follow-up, corroborating the efficacy of the treatment.

Assaf and colleagues first explored the neural architecture of GAD patients through fMRI. Then they treated 16 patients (9 = active; 7 = sham) with 30 sessions (5 days/week for 6 weeks) of low-frequency (1 Hz) rTMS over the right DLPFC [63], monitoring symptoms with PSQW and the Intolerance of Uncertainty Scale [64]. The results showed the "normalization" of functional connectivity of the dorsal anterior and the subgenual cingulate cortex, associated with an improvement in worry symptoms in patients treated with active rTMS.

Finally, Huang and co-workers conducted a randomized, double-blind, sham-controlled study on patients affected by GAD and comorbid insomnia [65]. Eighteen participants in the active group (out of a total of 36) were treated with 1 Hz rTMS over the right parietal cortex (PC), administering 6 sessions twice a week for 3 weeks. At the endpoint, 60% of the patients met the criteria for remission, defined as a HARS score less than 8. These results largely remained stable at 6-month follow-up.

13.7 TMS as Treatment of Agoraphobia

Agoraphobia is an anxiety disorder in which individuals develop marked anxiety or fear in situations like open spaces, public transportation or being outside of home alone. These patients tend to avoid these circumstances because of thoughts that escape might be difficult or even impossible [31].

To date, literature offers only a single study, where the selectd sample was mainly affected by PD and comorbid agoraphobia. This means that only limited conclusions can be drawn with regard to rTMS as a treatment for agoraphobia.

Deppermann et al. randomized 44 patients to the sham or active group, treating them with 15 sessions of iTBS over the left DLPFC in addition to 9 weeks of Cognitive Behavioral Therapy (CBT). Main outcome measures were evaluated with the PAS [46], the HARS and the Cardiac Anxiety Questionnaire (CAQ) [66]. Cortical activity was monitored through functional near-infrared spectroscopy (fNIRS) during an Emotional Stroop task, at baseline and post-iTBS. Clinical ratings significantly improved and remained stable at follow-up. However, no clinical differences between the active and the sham group were identified, except for a more stable reduction of agoraphobic avoidance during follow-up in the group treated with active iTBS.

13.8 Future Perspectives

TMS showed many significant and encouraging results for the treatment of patients with anxiety disorders. To date, except for conditions like agoraphobia or specific phobias, rTMS over the prefrontal cortex, with excitatory stimulation at the left side and/or inhibitory stimulation at the right side, can be considered effective to reduce anxiety symptoms in PD and GAD. However, the level of evidence available is considered low.

Several clinical features are implicated as possible confounding factors: limited sample size, the presence of psychiatric comorbidities (including mainly major depression) and heterogeneous psychotropic and psychotherapeutic concomitant

treatments. On the other hand, some methodological improvements must be taken into account to reach higher quality of evidence, including larger samples and extended periods of observation. One of the reasons for limited efficacy may be the reliance on a scalp-based method rather than neuronavigation based on individual MRI for targeting brain regions. Moving from anatomical to functional imaging positioning (e.g. fMRI, fNIRS) could allow achieving a greater efficacy for targeting TMS coils. Finally, coupling functional imaging with physiological parameters, such as skin conductance or heart rate variability, would allow better elucidation of the biological mechanisms underlying rTMS treatment.

Another methodological issue is the coil positioning site in the rTMS stimulation protocol. Looking at the "anxiety network" (Fig. 13.1), the sites of stimulation target of TMS therapeutic protocols are indeed limited mainly to PFC. In fact, areas such as the dmPFC or deeper areas such as those of cingulate cortices (dACC and aMCC) are not the targets of stimulation in TMS protocols to treat anxiety disorders (see Fig. 13.2). The use of the Double-Cone Coil or the H-coil in TMS therapeutic protocols for anxiety disorder treatment may extend the number of stimulation sites of "anxiety network", different from the "classical" DLPFC, allowing the modulation of deeper areas as dmPFC, anterior cingulate cortices and insulae.

To extend the field of TMS treatment for anxiety disorders, it would be interesting to investigate the clinical efficacy of TMS in special populations with anxiety disorders, such as elderly people, pregnant women, adolescents or drug abusers with comorbid anxiety, as well as all those comorbid medical conditions in which the treatment of anxiety with current therapeutic strategies is limited or contraindicated due to drug interactions. To date, only one case study has been conducted to investigate the role of rTMS in treating panic attacks during pregnancy: even though the results seem to be promising, it is premature to speculate about the efficacy of this protocol on such delicate patients [67]. Of note, Segev and colleagues tested rTMS on a 17-year-old adolescent who was admitted in the psychiatric ward due to intensified suicidal intention in comorbid MDD [68]. Interestingly, anxiety measures showed significant improvements, paving the way for future double-blind, sham-controlled clinical trials.

13.9 Conclusions

According to the literature reviewed in this chapter, therapeutic protocols using TMS were applied in approximately 370 subjects affected by, at least, one anxiety disorder. Consequently, until now, the level of evidence in the current guidelines is relatively low in relation to the clinical use of TMS therapeutic protocols in anxiety disorders, even though the clinical efficacy of rTMS in reducing anxiety symptom severity was consistently observed in PD and GAD. Future research, with refined methodological issues and study designs, is expected to reveal the real usefulness of TMS therapeutic protocols in the treatment of anxiety disorders.

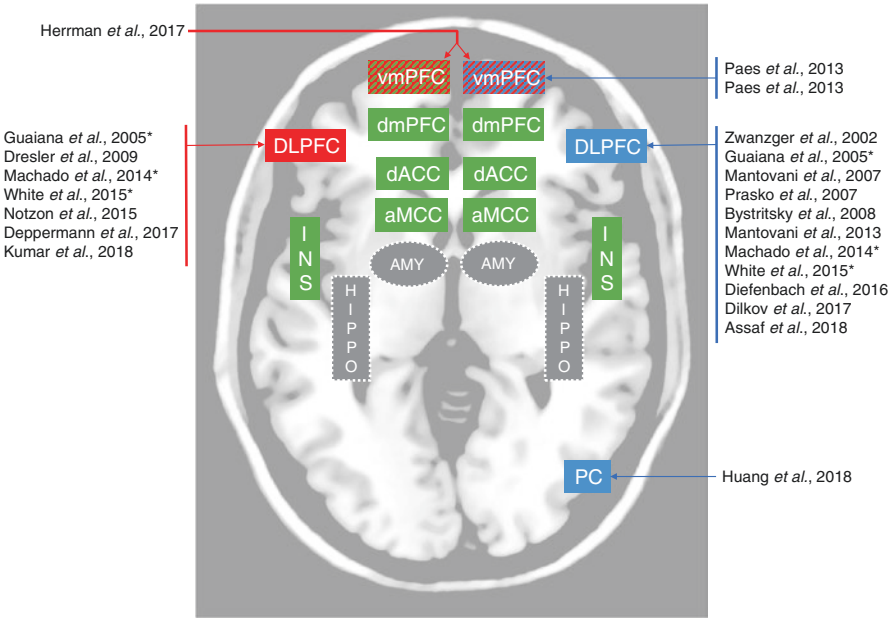

Fig. 13.2 Target brain areas for therapeutic TMS protocols in anxiety disorders. Red colour indicates those cortical areas where TMS coils were placed for implementing excitatory TMS protocols; blue colour indicates those areas where inhibitory TMS protocols were used; mixed colours indicate those areas where both excitatory and inhibitory TMS protocols were implemented. Green colour indicates brain structures involved in the "anxiety network" and potential sites of direct stimulation but not yet targeted by TMS protocols. Grey colour indicates the deepest areas of the "anxiety network" that cannot be directly stimulated by TMS protocols. *aMCC* anterior midcingulate cortex, *AMY* amygdala, *dACC* dorsal anterior cingulate cortex, *DLPFC* dorsolateral prefrontal cortex, *dmPFC* dorsomedial prefrontal cortex, *HIPPO* hippocampus, *INS* insula, *vmPFC* ventromedial prefrontal cortex

References

1. Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: a systematic review and meta-regression. Psychol Med. 2013;43(5):897–910.
2. Baxter AJ, Vos T, Scott KM, Ferrari AJ, Whiteford HA. The global burden of anxiety disorders in 2010. Psychol Med. 2014;44(11):2363–74.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
4. Kessler RC, Angermeyer M, Anthony JC, De Graaf R, Demyttenaere K, Gasquet I, et al. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry. 2007;6(3):168–76.
5. Beesdo K, Knappe S, Pine DS. Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V. Psychiatr Clin North Am. 2009;32(3):483–524.
6. Silove D, Alonso J, Bromet E, Gruber M, Sampson N, Scott K, et al. Pediatric-onset and adult-onset separation anxiety disorder across countries in the world mental health survey. Am J Psychiatry. 2015;172(7):647–56.

7. Zhang X, Norton J, Carriere I, Ritchie K, Chaudieu I, Ancelin ML. Generalized anxiety in community-dwelling elderly: prevalence and clinical characteristics. J Affect Disord. 2015;172:24–9.
8. Kessler RC, Ruscio AM, Shear K, Wittchen HU. Epidemiology of anxiety disorders. Curr Top Behav Neurosci. 2010;2:21–35.
9. McLean CP, Asnaani A, Litz BT, Hofmann SG. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. J Psychiatr Res. 2011;45(8): 1027–35.
10. Beesdo-Baum K, Knappe S. Developmental epidemiology of anxiety disorders. Child Adolesc Psychiatr Clin N Am. 2012;21(3):457–78.
11. Robinson OJ, Pike AC, Cornwell B, Grillon C. The translational neural circuitry of anxiety. J Neurol Neurosurg Psychiatry. 2019;90(12):1353–60.
12. McTeague LM, Huemer J, Carreon DM, Jiang Y, Eickhoff SB, Etkin A. Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. Am J Psychiatry. 2017;174(7):676–85.
13. Drevets WC, Savitz J, Trimble M. The subgenual anterior cingulate cortex in mood disorders. CNS Spectr. 2008;13(8):663–81.
14. Jaworska N, Yucel K, Courtright A, MacMaster FP, Sembo M, MacQueen G. Subgenual anterior cingulate cortex and hippocampal volumes in depressed youth: the role of comorbidity and age. J Affect Disord. 2016;190:726–32.
15. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry. 2007;164(10):1476–88.
16. Notzon S, Deppermann S, Fallgatter A, Diemer J, Kroczek A, Domschke K, et al. Psychophysiological effects of an iTBS modulated virtual reality challenge including participants with spider phobia. Biol Psychol. 2015;112:66–76.
17. Prasko J, Horacek J, Zalesky R, Kopecek M, Novak T, Paskova B, et al. The change of regional brain metabolism (18FDG PET) in panic disorder during the treatment with cognitive behavioral therapy or antidepressants. Neuro Endocrinol Lett. 2004;25(5):340–8.
18. Duval ER, Javanbakht A, Liberzon I. Neural circuits in anxiety and stress disorders: a focused review. Ther Clin Risk Manag. 2015;11:115–26.
19. Asok A, Kandel ER, Rayman JB. The neurobiology of fear generalization. Front Behav Neurosci. 2018;12:329.
20. Vytal KE, Overstreet C, Charney DR, Robinson OJ, Grillon C. Sustained anxiety increases amygdala-dorsomedial prefrontal coupling: a mechanism for maintaining an anxious state in healthy adults. J Psychiatry Neurosci. 2014;39(5):321–9.
21. Myers KM, Davis M. Mechanisms of fear extinction. Mol Psychiatry. 2007;12(2):120–50.
22. Lang S, Kroll A, Lipinski SJ, Wessa M, Ridder S, Christmann C, et al. Context conditioning and extinction in humans: differential contribution of the hippocampus, amygdala and prefrontal cortex. Eur J Neurosci. 2009;29(4):823–32.
23. Milad MR, Quirk GJ. Fear extinction as a model for translational neuroscience: ten years of progress. Annu Rev Psychol. 2012;63:129–51.
24. Alvarez RP, Chen G, Bodurka J, Kaplan R, Grillon C. Phasic and sustained fear in humans elicits distinct patterns of brain activity. Neuroimage. 2011;55(1):389–400.
25. Brinkmann L, Buff C, Feldker K, Tupak SV, Becker MPI, Herrmann MJ, et al. Distinct phasic and sustained brain responses and connectivity of amygdala and bed nucleus of the stria terminalis during threat anticipation in panic disorder. Psychol Med. 2017;47(15): 2675–88.
26. Carlsson K, Andersson J, Petrovic P, Petersson KM, Ohman A, Ingvar M. Predictability modulates the affective and sensory-discriminative neural processing of pain. Neuroimage. 2006;32(4):1804–14.
27. Shankman SA, Gorka SM, Nelson BD, Fitzgerald DA, Phan KL, O'Daly O. Anterior insula responds to temporally unpredictable aversiveness: an fMRI study. Neuroreport. 2014;25(8):596–600.

28. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci. 2007;27(9):2349–56.
29. Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ. The integration of negative affect, pain and cognitive control in the cingulate cortex. Nat Rev Neurosci. 2011;12(3):154–67.
30. Uddin LQ. Salience processing and insular cortical function and dysfunction. Nat Rev Neurosci. 2015;16(1):55–61.
31. American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Association; 2013. xliv, 947 p.
32. Olatunji BO, Woods CM, de Jong PJ, Teachman BA, Sawchuk CN, David B. Development and initial validation of an abbreviated Spider Phobia Questionnaire using item response theory. Behav Ther. 2009;40(2):114–30.
33. Szymanski J, O'Donohue W. Fear of Spiders Questionnaire. J Behav Ther Exp Psychiatry. 1995;26(1):31–4.
34. Haidt J, McCauley C, Rozin P. Individual differences in sensitivity to disgust: a scale sampling seven domains of disgust elicitors. Pers Individ Differ. 1994;16(5):701–13.
35. Wolpe J. The practice of behavior therapy. 2nd ed. Oxford: Pergamon; 1973. xvi, 318-xvi, p.
36. Reiss S, Peterson RA, Gursky DM, McNally RJ. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. Behav Res Ther. 1986;24(1):1–8.
37. Perna G, Riva A, Defillo A, Sangiorgio E, Nobile M, Caldirola D. Heart rate variability: can it serve as a marker of mental health resilience? J Affect Disord. 2020;263:754–61.
38. Herrmann MJ, Katzorke A, Busch Y, Gromer D, Polak T, Pauli P, et al. Medial prefrontal cortex stimulation accelerates therapy response of exposure therapy in acrophobia. Brain Stimul. 2017;10(2):291–7.
39. Paes F, Machado S, Arias-Carrion O, Silva AC, Nardi AE. rTMS to treat social anxiety disorder: a case report. Braz J Psychiatry. 2013;35(1):99–100.
40. Beck A, Emery G. Anxiety disorders and phobias: a cognitive perspective. New York: Basic Books; 1985. p. 368.
41. Riggio RE. Assessment of basic social skills. J Pers Soc Psychol. 1986;51(3):649–60.
42. Paes F, Baczynski T, Novaes F, Marinho T, Arias-Carrion O, Budde H, et al. Repetitive transcranial magnetic stimulation (rTMS) to treat social anxiety disorder: case reports and a review of the literature. Clin Pract Epidemiol Ment Health. 2013;9:180–8.
43. Liebowitz MR. Social phobia. Mod Probl Pharmacopsychiatry. 1987;22:141–73.
44. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561–71.
45. Zwanzger P, Minov C, Ella R, Schule C, Baghai T, Moller HJ, et al. Transcranial magnetic stimulation for panic. Am J Psychiatry. 2002;159(2):315–6.
46. Bandelow B, Brunner E, Beinroth D, Pralle L, Broocks A, Hajak G, et al. Application of a new statistical approach to evaluate a clinical trial with panic disorder patients. Eur Arch Psychiatry Clin Neurosci. 1999;249(1):21–7.
47. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32(1):50–5.
48. Guaiana G, Mortimer AM, Robertson C. Efficacy of transcranial magnetic stimulation in panic disorder: a case report. Aust N Z J Psychiatry. 2005;39(11–12):1047.
49. Dresler T, Ehlis AC, Plichta MM, Richter MM, Jabs B, Lesch KP, et al. Panic disorder and a possible treatment approach by means of high-frequency rTMS: a case report. World J Biol Psychiatry. 2009;10(4 Pt 3):991–7.
50. Machado S, Santos V, Paes F, Arias-Carrion O, Carta MG, Silva AC, et al. Repetitive transcranial magnetic stimulation (rTMS) to treat refractory panic disorder patient: a case report. CNS Neurol Disord Drug Targets. 2014;13(6):1075–8.
51. Mantovani A, Lisanby SH, Pieraccini F, Ulivelli M, Castrogiovanni P, Rossi S. Repetitive transcranial magnetic stimulation (rTMS) in the treatment of panic disorder (PD) with comorbid major depression. J Affect Disord. 2007;102(1–3):277–80.

52. Sheenan DV. The anxiety disease. New York: Charles Scribner & Sons; 1983. 151 p.
53. Mantovani A, Aly M, Dagan Y, Allart A, Lisanby SH. Randomized sham controlled trial of repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex for the treatment of panic disorder with comorbid major depression. J Affect Disord. 2013;144(1–2):153–9.
54. Prasko J, Zalesky R, Bares M, Horacek J, Kopecek M, Novak T, et al. The effect of repetitive transcranial magnetic stimulation (rTMS) add on serotonin reuptake inhibitors in patients with panic disorder: a randomized, double blind sham controlled study. Neuro Endocrinol Lett. 2007;28(1):33–8.
55. Kumar S, Singh S, Parmar A, Verma R, Kumar N. Effect of high-frequency repetitive transcranial magnetic stimulation (rTMS) in patients with comorbid panic disorder and major depression. Australas Psychiatry. 2018;26(4):398–400.
56. Bystritsky A, Kaplan JT, Feusner JD, Kerwin LE, Wadekar M, Burock M, et al. A preliminary study of fMRI-guided rTMS in the treatment of generalized anxiety disorder. J Clin Psychiatry. 2008;69(7):1092–8.
57. White D, Tavakoli S. Repetitive transcranial magnetic stimulation for treatment of major depressive disorder with comorbid generalized anxiety disorder. Ann Clin Psychiatry. 2015;27(3):192–6.
58. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092–7.
59. Diefenbach GJ, Bragdon LB, Zertuche L, Hyatt CJ, Hallion LS, Tolin DF, et al. Repetitive transcranial magnetic stimulation for generalised anxiety disorder: a pilot randomised, double-blind, sham-controlled trial. Br J Psychiatry. 2016;209(3):222–8.
60. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the Penn State Worry Questionnaire. Behav Res Ther. 1990;28(6):487–95.
61. Diefenbach GJ, Assaf M, Goethe JW, Gueorguieva R, Tolin DF. Improvements in emotion regulation following repetitive transcranial magnetic stimulation for generalized anxiety disorder. J Anxiety Disord. 2016;43:1–7.
62. Dilkov D, Hawken ER, Kaludiev E, Milev R. 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. Prog Neuropsychopharmacol Biol Psychiatry. 2017;78:61–5.
63. Assaf M, Rabany L, Zertuche L, Bragdon L, Tolin D, Goethe J, et al. Neural functional architecture and modulation during decision making under uncertainty in individuals with generalized anxiety disorder. Brain Behav. 2018;8(8):e01015.
64. Freeston MH, Rhéaume J, Letarte H, Dugas MJ, Ladouceur R. Why do people worry? Pers Individ Differ. 1994;17(6):791–802.
65. Huang Z, Li Y, Bianchi MT, Zhan S, Jiang F, Li N, et al. Repetitive transcranial magnetic stimulation of the right parietal cortex for comorbid generalized anxiety disorder and insomnia: a randomized, double-blind, sham-controlled pilot study. Brain Stimul. 2018;11(5):1103–9.
66. Eifert GH, Thompson RN, Zvolensky MJ, Edwards K, Frazer NL, Haddad JW, et al. The cardiac anxiety questionnaire: development and preliminary validity. Behav Res Ther. 2000;38(10):1039–53.
67. Nahas Z, Bohning DE, Molloy MA, Oustz JA, Risch SC, George MS. Safety and feasibility of repetitive transcranial magnetic stimulation in the treatment of anxious depression in pregnancy: a case report. J Clin Psychiatry. 1999;60(1):50–2.
68. Segev A, Spellun J, Bloch Y. Anxiety as a central outcome measure in an adolescent with major depressive disorder treated with repetitive transcranial magnetic stimulation. J ECT. 2014;30(4):e54–5.