



A systematic review on the therapeutic effectiveness of non-invasive brain stimulation for the treatment of anxiety disorders

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ARTICLE INFO

Keywords:

Non-invasive brain stimulation
rTMS
tDCS
Specific phobias
Social anxiety disorder
Panic disorder
Agoraphobia
Generalized anxiety disorder

ABSTRACT

The interest in the use of non-invasive brain stimulation for enhancing neural functions and reducing symptoms in anxiety disorders is growing. Based on the DSM-V classification for anxiety disorders, we examined all available research using repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) for the treatment of specific phobias, social anxiety disorder, panic disorder, agoraphobia, and generalized anxiety disorder. A systematic literature search conducted in PubMed and Google Scholar databases provided 26 results: 12 sham-controlled studies and 15 not sham-controlled studies. With regard to the latter sub-group of studies, 9 were case reports, and 6 open label studies. Overall, our work provides preliminary evidence that both, excitatory stimulation of the left prefrontal cortex and inhibitory stimulation of the right prefrontal cortex can reduce symptom severity in anxiety disorders. The current results are discussed in the light of a model for the treatment for anxiety disorders via non-invasive brain stimulation, which is based on up-/downregulation mechanisms and might serve as guide for future systematic investigations in the field.

1. Introduction

Exploring new avenues for the treatment of mental disorders through non-pharmacological and/or non-invasive intervention approaches is of growing interest in the neuroscience community. This interest is motivated by the hope to deal with drug-treatment resistant disorders, to provide effective treatments in case of concurrent medical conditions that prevent standard treatments and to enhance efficacy of therapies by combining standard treatment approaches with non-invasive brain stimulation. One goal of research endeavours is to identify methodologies for the management of neuropsychiatric disorders that combine both therapeutic efficacy and tolerability. Since pathologically altered neural plasticity is an important component of many neurological and psychiatric diseases, non-invasive stimulation of the brain is an potential treatment option, as it is able to modulate neural activity (e.g., Kronberg et al., 2017; Ziemann, 2017) by acting on synaptic plasticity (Fritsch et al., 2010; Kronberg et al., 2017; Nitsche et al., 2012b). The precise underlying mechanisms of non-invasive brain

stimulation-induced synaptic plasticity have still to be clarified. Yet, evidence suggests that respective plasticity is linked to long-term potentiation (LTP) and long-term depression (LTD) (e.g., Monte-Silva et al., 2013; Nitsche et al., 2003; see also Bliss and Cooke, 2011).

Several review articles suggest therapeutic efficacy of non-invasive brain stimulation for the treatment of a wide range of neurological and psychiatric disorders, such as depression (Mutz et al., 2018), addiction (Feil and Zangen, 2010) and epilepsy (Cooper et al., 2018) in both pediatric and adult populations. For more extensive reviews in the field see also (Flöel, 2014; Kuo et al., 2014; Martin et al., 2017; Rivera-Urbina Guadalupe et al., 2017; Vicario and Nitsche, 2013a, Vicario and Nitsche, 2013b). In the current article, we aim to provide a systematic review on therapeutic effects of non-invasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), on anxiety disorders in adult populations, such as specific phobias (SP), social anxiety disorder (SAD), panic disorder (PD), agoraphobia, and generalized anxiety disorder (GAD). In the context of this review, it is worthwhile noting that

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<https://doi.org/10.1016/j.neubiorev.2018.12.012>

Received 26 August 2018; Received in revised form 4 December 2018; Accepted 8 December 2018

Available online 10 December 2018

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post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) are no longer listed under the anxiety disorders category by the Diagnostic and Statistical Manual of Mental Disorders (DSM) Fifth Edition (Association, A.P., 2014, 2014; see also (Craske et al., 2017). We did not examine the effects of non-invasive brain stimulation on these syndromes because these disorders have been comprehensively addressed in several recent systematic reviews and/or meta-analyses (e.g., Berlim et al., 2013; Brunelin et al., 2018; Yan et al., 2017; Zhou et al., 2017).

We provide a brief introduction concerning the basic physiological principles underlying the effects of the mentioned non-invasive brain stimulation techniques. However, is not an aim of this review to address this aspect in detail. More exhaustive/detailed overviews are provided by several specialized reviews in the field (Klomjai et al., 2015a, b; Polanía et al., 2018; Valero-Cabré et al., 2017; Woods et al., 2016; Yavari et al., 2018).

tDCS is a well-established neurostimulation technique that allows stimulation of the cerebral cortex in a safe and non-invasive way. Stimulation is conducted via two or more electrodes with opposite polarities (i.e., anodal and cathodal) placed on the scalp and connected with a battery-driven constant current stimulator with a maximum output in the milliamperes (mA) range. A relatively weak electrical direct current (usually 1 ~ 2 mA) is applied via the electrodes, and a proportion of it enters the brain (Nitsche et al., 2008, 2003; Nitsche and Paulus, 2000). At the macroscopic level, anodal (A) stimulation increases cortical excitability, whereas cathodal (C) stimulation decreases it (Stagg and Nitsche, 2011). However, the impact and directionality of the effects of tDCS on cortical excitability are also influenced by stimulation intensity, as suggested by the study by Batsikadze et al. (2013) where both anodal and cathodal tDCS at 2 mA increased corticospinal excitability, whereas 1 mA cathodal tDCS decreased it. The effects on cortical excitability can last for up to 90 min after a single stimulation session of 13 ~ 20 min duration (Nitsche and Paulus, 2000), and can be further extended by repeated stimulation (i.e., cumulative effects) (Monte-Silva et al., 2013). The physiological aftereffects of prolonged (i.e., application for several minutes) anodal and cathodal tDCS are dependent on synaptic modulation. This assumption is supported by pharmacological studies in humans (Nitsche et al., 2012a) and animal models (Fritsch et al., 2010; Kronberg et al., 2017). For example, enhanced long-term potentiation (LTP) in basal dendrites of rat hippocampal slices has been documented in response to anodal stimulation (Kronberg et al., 2017). Anodal stimulation increases intracortical facilitation (ICF), and its after-effects are prevented by NMDA receptor blockade, but enhanced by respective receptor agonists (Liebetanz et al., 2002; Nitsche et al., 2003, 2004; Nitsche et al., 2005). NMDA receptor block can also prevent cathodal tDCS-generated after-effects (Nitsche et al., 2003). Given the role of the glutamatergic receptor on ICF (Keller, 1993), it can, therefore, be assumed that glutamatergic neurons are crucial for the induction of plasticity by tDCS. Moreover, tDCS-induced glutamatergic plasticity might be prompted by tDCS-generated alterations of GABA activity. This is suggested by a magnetic resonance spectroscopy (MRS) study documenting a reduction of GABA content of the motor cortex (Stagg et al., 2009) following both anodal and cathodal tDCS.

rTMS is another non-invasive and safe brain stimulation technique based on the application of trains of magnetic pulses over a target cortical region, through the use of a copper coil placed over the scalp, which induces electrical pulses at the brain level. The application of trains of multiple pulses of TMS with a short inter-stimulus interval induces a long-lasting change on cortical excitability (Pascual-Leone et al., 1994). In this regard, it is important to distinguish between low and high-frequency rTMS. Generally speaking, appropriate intensity of low frequency (1–5 Hz) rTMS decreases cortical excitability, while an appropriate intensity of high-frequency rTMS (> 5 Hz) increases cortical excitability (Pell et al., 2011). Theta Burst stimulation (TBS) is another rTMS protocol, which induces similar effects as conventional

rTMS, but requires less time. Generally speaking, Intermittent TBS (iTBS) produces excitatory effects, whereas continuous TBS (cTBS) produces a reduction of cortical excitability (Li et al., 2014). LTP- and LTD-like mechanisms seem to be involved also in rTMS-induced after-effects (Ziemann et al., 2008. See also Müller-Dahlhaus and Vlachos, 2013 for a review). Vlachos et al. (2012) reported functional and structural changes of CA1 pyramidal neurons of entorhino-hippocampal slice cultures following repetitive magnetic stimulation. Research in rodent models provides relevant insights in the molecular mechanisms associated with rTMS. Wang et al. (2011) have documented an increment of brain-derived neurotrophic factor (BDNF) binding affinity with NMDA receptors in the rat prefrontal cortex (PFC) in response to 5 days of rTMS. Importantly, BDNF plays a key role in the regulation of synaptic strength and mediation of neural plasticity (Bramham and Messaoudi, 2005).

The main goal of this article is to provide a state-of-the-art review on the therapeutic benefits of non-invasive brain stimulation in anxiety disorders. According to recent suggestions (e.g., Månsson et al., 2016), one important pathological mechanism in anxiety disorders is maladaptive structural and functional neuroplasticity of prefrontal and limbic regions. It is suggested that anxiety is associated with a hypoactivation of the left DLPFC (e.g., Amit Etkin and Wager, 2007; Nishimura et al., 2007), which inhibits the amygdala, a neural structure involved in threat detection and processing, which is elevated across most anxiety disorders (Notzon et al., 2015). On the other hand, there is evidence for higher activation of the right DLPFC in Anxiety disorders, such as panic disorder (Nordahl et al., 1998; Prasko et al., 2004). These atypical functional activation patterns might be also associated with respective structural abnormalities of these neural regions, which might contribute to the emergence and chronicity of cognitive/emotional deficits (i.e., exaggerated fear response/threat perception). For instance, it was provided evidence of amygdalar and volume alterations in social anxiety, possibly associated with symptom severity (Machado-de-Sousa et al., 2014). In line with these premises, non-invasive brain stimulation might be a helpful treatment approach, via counteracting respective dysregulated activity and maladaptive neuroplasticity by modulating pathological hypo-/hyper-activation patterns of the DLPFC in respective clinical populations, as described above. In the discussion section of this review, we also outline a treatment model for anxiety disorders via non-invasive brain stimulation, which is conceptually based on up-/downregulation mechanisms and might serve as guide for future systematic investigations in the field.

This review will help to clarify i) whether and to what extent non-invasive brain stimulation is an effective treatment of different anxiety disorders, and ii) which combination in terms of stimulation type (i.e., inhibitory vs. excitatory) and cortical target is suited for the therapy of anxiety disorders. Moreover, it will provide information about relevant stimulation parameters as a starting point for systematic optimization, as well as generate hypotheses how non-invasive brain stimulation might be combined with other interventions to obtain improved therapeutic benefits.

2. Methods

Data for this systematic review were collected in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Moher et al., 2010). The PRISMA consists of a checklist intended to facilitate preparation and reporting review/meta-analysis studies by identifying, selecting, and critically appraising relevant research, and collecting and analyzing data from the studies that are included in the review.

2.1. Eligibility criteria

To ensure a high level of methodological accuracy, only peer-reviewed published studies conducted in humans were included in our

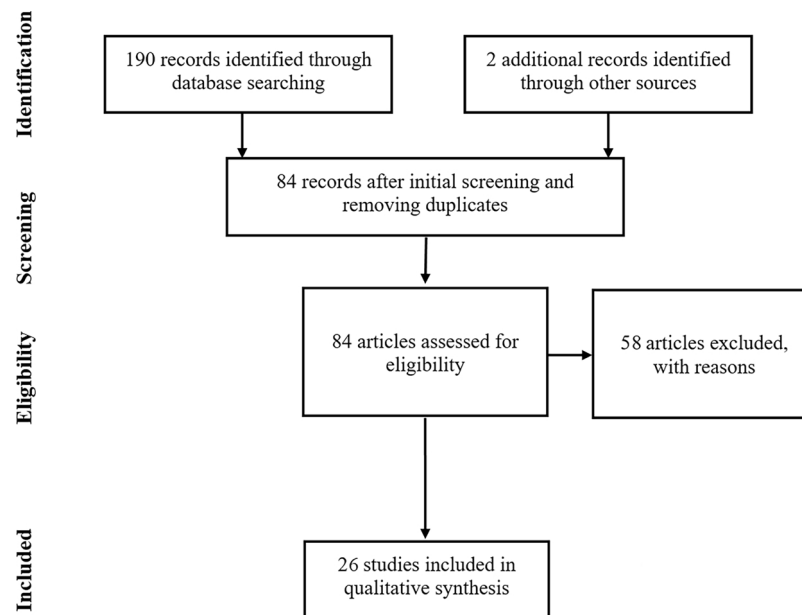


Fig. 1. PRISMA flow diagram selected for qualitative analysis of the respective studies.

analysis. The inclusion criteria were: (i) original research articles published in English language in peer-reviewed journals; (ii) studies conducted in patients with anxiety disorders according to criteria mentioned in the DSM-5 edition; (iii) detailed description of the stimulation method; (iv) studies exploring rTMS and tDCS as an intervention. Exclusion criteria were: i) studies where anxiety symptoms of the patients were caused by specific medical conditions and/or drug consumption; ii) review articles; iii) articles not referring to the subject of interest (i.e., anxiety disorders) and/or not addressing therapeutic goal.

2.2. Search strategy and study selection

A comprehensive literature search was conducted in PubMed and Google Scholar databases with the final search updated on July 2018. The initial search conducted used the keywords (rTMS, tDCS, SP, SAD, PD, agoraphobia, and GAD) and identified a total of 190 articles which were reduced to 84 records after initial screening and removing duplicates (See Fig.1). The remaining records were then assessed for eligibility. According to this screening, the final number of articles included in the review was 26: 12 sham-controlled studies and 15 not sham-controlled studies. With regard to the latter sub-group of studies, 8 were case reports, and 6 open label studies. We decided to include not-sham controlled, single case and open label studies to provide the reader with a more comprehensive overview of the current research in the field. Details are reported on Table 1.

The search was conducted by coupling the full word/acronym of one of the two techniques (i.e., -rTMS- and tDCS) with one of the five anxiety disorders mentioned above. This way we obtained ten pairs of words which provided the following outputs: n 2 articles for the pair “rTMS + SP”; n 15 for the pair “rTMS + SAD” (13 articles were excluded: 3 articles were referring to animal research; 5 articles were referring to no SAD research; 1 article did not address therapeutic purposes; 4 articles were reviews); n 28 for the pair “rTMS + PD” (19 articles were excluded: 2 articles were referring to drug treatment; 1 article tested healthy humans with a PD-inducing protocol; 5 articles were referring not to PD research or rTMS treatment; 11 articles were reviews; 1 article was written in Spanish; in 1 article PD was not assessed as primary disorder and outcome); n 3 articles for the pair “rTMS + agoraphobia” (2 were excluded: 1 did not address therapeutic purposes; 1 was a review article); n 23 articles for the pair “rTMS + GAD” (15 were excluded: 10 articles were reviews; 4 articles

were referring not to GAD research; 1 article was referring not to therapeutic research); n 1 article for the pair “tDCS + SP”; n 3 articles for the pair “tDCS + SAD” (2 were excluded: 1 was a review article; 1 was not referring to SAD); n 4 articles for the pair “tDCS + PD” (3 were excluded: 2 were review articles; 1 was not referring to PD); n 0 for the pair “tDCS + Agoraphobia”; n 5 for the pair “tDCS + GAD” (2 were excluded: 1 was a review article; 1 was not referring to GAD).

2.3. Risk of bias across studies

Across the included studies in this review, a potential database bias should be considered. Only articles within databases in English language were used, which might have compromised access to articles published in other languages.

3. Anxiety disorders

In the next paragraphs, we address the therapeutic effects of non-invasive brain stimulation on anxiety disorders. According to the DSM-5 (Association, A.P., 2014), anxiety disorders include separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, panic disorder, agoraphobia and generalized anxiety disorder. We did not consider separation anxiety disorder and selective mutism, as these are specific childhood syndromes.

3.1. Specific phobias

According to the DSM-5 (Association, A.P., 2014), the term Specific Phobias (SP) refers to a clinical condition characterized by marked fear, anxiety or avoidance of specific circumstances/situations, such as animals, environments, and others.

The first TMS study on SP was performed by Notzon et al. (2015), who conducted a single-blind, sham-controlled parallel group study in 41 participants with spider phobia and 40 healthy controls (age range 18–65) exposed to spiders in a virtual reality scenario. The authors applied one session of intermittent Theta Burst Stimulation (iTBS), whose effects are comparable to high-frequency rTMS (Huang et al., 2005), over the left DLPFC (for more details on this and the following studies see Table 1). For the assessment of spider fear symptoms, the authors used several self-reported measures such as the Fear of Spiders Questionnaire (FSQ) (Szymanski and O'Donohue, 1995) and the Spider

Table 1

A total of 475 participants were involved in all 26 studies, including 412 patients and 63 controls. DLPFC = dorsolateral prefrontal cortex; mPFC = medial prefrontal cortex; vmPFC = ventromedial prefrontal cortex; iTBS = intermittent theta burst stimulation; rTMS = repetitive transcranial magnetic stimulation; LF = Low frequency; HF = High frequency; MT = motor threshold; AMT = active motor threshold; RMT = resting motor threshold; SPQ = Spider Phobia Questionnaire; ASI = Anxiety Sensitivity Index; AQ = acrophobia questionnaire; BAT = Behavioral Avoidance Test; VSS = Vertigo Symptom Scale; SAD = Social Anxiety Disorder; SSI = Social Skills Inventory; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; LSAS = Liebowitz social anxiety scale; API = Acute Panic Inventory; PSS = Panic Symptom Scale; HAS = Hamilton Anxiety Scale; PAS = Panic and Agoraphobia Scale; PDSS = Panic Disorder Severity Scale; HDS = Hamilton Depression scale; HDRS = Hamilton Rating Scale for Depression; HAMA = Hamilton Rating Scale for Anxiety; SCRAS = Sheehan Clinician Rated Anxiety Scale; CAQ = Cardiac Anxiety Questionnaire; FADAS = Four-dimensional Anxiety and Depression Scale; PGI-T = Patient Global Impression of Improvement; CGI-S = Clinical Global Impression – severity scale; CGI-I = The CGI – improvement scale; PSWQ = Penn State Worry Questionnaire; PSQI = Pittsburgh Sleep Quality Index; N/A = not applicable; NR = not reported * = same as in the previous reference.

#	Authors	N	Gender M/F	Mean age ± SD	Stimulation site	Pulses per session	TMS coil	Frequency / Intensity
Specific phobia								
Notzon et al. (2015)	Spider phobia (N = 41)/ healthy control (N = 40)	9/72		26.46 ± 8.47 [range 18–65]	Left DLPFC (F3)	600	8-figure	15 Hz / 80% RMT
(Heeren et al., 2017) (Palm et al., 2018)	Acrophobia (N = 39) phobic postural vertigo (N = 8)	13/26 5/3		46.6 ± 13.17 45.6 ± 12.3 [range 24–59]	mPFC (FP2) Left DLPFC (F3)	1560 N/A	8-figure N/A	10 Hz / 100% RMT 2 mA
Social Anxiety disorder								
Paes et al. (2013a)	SAD (N = 1)	1/0			Right (vmPFC)	1500	8-figure	1 Hz / 120% MT
Paes et al. (2013b)	SAD (N = 2)	1/1			Right (vmPFC)	1500	8-figure	1 Hz / 120% MT
Heeren et al. (2017)	SAD (N = 19)	0/19		24.16 ± 4.87	Left DLPFC (F3)	N/A	N/A	2 mA
Panic disorder (PD)								
Zwanzger et al. (2002)	N = 1	0/1		52	right DLPFC (F4)	1200	8-figure	1 Hz / 110% NR
Guaiana et al. (2005)	N = 1	0/1		34	Right and left frontal cortex	600 1620	8-figure	1 Hz / 100% MT
Dresler et al. (2009)	N = 1	1/0		44	Left DLPFC (F3)	2400	8-figure	20 Hz / 110% MT
Machado et al. (2014)	N = 1	0/1		34	Right & Left DLPFC (F4, F3)	1000/ right H. /left H NR.	8-figure	1 Hz / 100 120% MT 10 Hz / 100 120% MT
Mantovani et al. (2007)	N = 6	3/3		50 ± 18.46	Right DLPFC (F4)	1200	8-figure	1 Hz / 100% RMT
Prasko et al. (2007)	N = 15	4/11		33.7 ± 9.2	Right DLPFC (F4)	1800	8-figure	1 Hz / 110% MT
Mantovani et al. (2013)	N = 25	12/13		40 ± 11.6	Right DLPFC (F4)	1800	8-figure	1 Hz / 110% RMT
Kumar et al. (2018)	N = 13	NR		[range 28–52]	Left DLPFC (F3)	1000	8-figure	20 Hz / 110% RMT
Shiozawa et al. (2014a)	N = 1	0/1		44	Right DLPFC (F4)	N/A	N/A	2mA
(Deppermann et al., 2017)	PD with/without agoraphobia (N = 44), healthy control (N = 23)	17/27		33.5 [range 18–65]	Left DLPFC (F3)	600	8-figure	15 Hz / 80% RMT
Agoraphobia								
Generalized anxiety disorder								
Bystritsky et al. (2008)	N = 10	5/5		45.30 ± 12.1 [range 18–56]	Right DLPFC (F4)	900	8-figure	1 Hz / 90% RMT
Bystritsky et al. (2009)* (White and Tavakoli, 2015)	N = 10 N = 13	5/5 5/8		45.30 ± 12.1 [range 18–56] 42.46	Right DLPFC (F4) Right & left DLPFC (F4 & F3)	900 1000	8-figure 8-figure	1 Hz / 90% RMT 1 Hz 10 Hz / NR
Diefenbach et al. (2016a)	N = 25	6/19		44.29 ± 13.35	Right DLPFC (F4)	900	8-figure	1 Hz / 90% RMT
(Diefenbach et al., 2016b, * Dilkov et al. (2017))	N = 25 N = 40	6/19 21/19		44.29 ± 13.35 36 ± 8.5 [range 18–65]	Right DLPFC (F4) Right DLPFC (F4)	900 1600	8-figure 8-figure	1 Hz / 90% RMT 20 Hz / 110% RMT (continued on next page)

Table 1 (continued)

#	Authors	N	Gender M/F	Mean age ± SD	Stimulation site	Pulses per session	TMS coil	Frequency / Intensity
	Huang et al. (2018) (Assaf et al., 2018)	N = 36	18/18	45.08 ± 11.24 [range 18–65]	Right parietal (P4)	1500	8-figure	1 Hz / 90% RMT
	Shiozawa et al. (2014b)	N = 16	7/24	43.07	Right DLPFC (F4)	900	8-figure	1 Hz / 90% RMT
		N = 1	0/1	58	Right DLPFC (F4)	N/A	N/A	2mA
	Movahed et al. (2018)	N = 18	10/8	28.73 ± 9.6	Right DLPFC (F4)	N/A	N/A	2mA
#	Duration	NIBS type	polarity / electrode size	Control	Measure	Outcome	Outcome direction	Study type (blinding)
Specific phobia								
3 min	rTMS (iTBS)	N/A		Sham	SPQ / ASI	Change in SPQ / ASI scores	No changes in symptoms	RCT (single blind) successful p = 1.0, p = 0.52
2 x 20 min	HF rTMS	N/A		Sham	AQ /BAT	Change in AQ	Symptom improvement	RCT (double blind) successful p = 0.52
5 x 30 min	tDCS	anodal F3-cathodal Fp2 / 35 cm ²		No control	VSS	Change in VSS scores	Partial symptom improvement	Open label study
Social Anxiety disorder								
25 min	LF rTMS	N/A		No control	SSI /BDI / BAI	Change in SSI, BDI, BAI scores	Symptom improvement	case study (pre, post, follow-up)
12 x 25 min	LF rTMS	N/A		No control	LSAS /BDI / BAI	Change in LSAS, BDI, BAI scores	Symptom improvement	Single subject design (pre, post, follow-up)
25 min	tDCS	anodal F3-cathodal left arm / 35 cm ²		Sham	Dot probe task (online)	Change in attention bias	Decrease in attention bias	RCT (double blind)
Panic disorder (PD)								
10 x NR	rTMS	N/A		No control	ACI / PSS / HAS / PAS	Change in ACI, PSS, HAS, PAS scores	Symptom improvement	case study
9 x NR	LF & HF rTMS	N/A		No control	PDSS	Change in PDSS	Symptom improvement after HF rTMS	case study (follow-up)
20 x NR	HF rTMS	N/A		No control	HDS / Emotional Stroop task	Change in HDS, Stroop accuracy	No changes in task performance	case study (follow-up)
12 x 15 min	LF & HF rTMS	N/A	N/A	No control	BAI / PDSS	Change in BAI, PDSS	Symptom improvement	case study (follow-up)
10 x 28 min	LF rTMS	N/A		No control	PDSS / HAS / HDS /SCRAS	Change in PDSS, SCRAS, HAS	Symptom improvement	Open label trial (6-month follow-up)
10 x 30 min	LF rTMS	N/A		Sham	PDSS / BAI / HAMA	Change in PDSS, BAI, HAMA	Symptomsimprovement after active / sham rTMS	RCT (double blind)
40 x 30 min	LF rTMS	N/A		Sham	PDSS / HDRS	Change in PDSS, HDRS	Symptomsimprovement	unsuccessful outcome
20 x 4 min	HF rTMS	N/A		No control	PDSS / HDRS	Change in PDSS, HDRS	Symptom improvement	RCT (double blind) successful at 80%
10 x 30 min	tDCS	cathodal F4-anodal left deltoid / 25 cm ²		No control	HAS / BAI	Change in HAS, BAI	Symptom improvement	Open label design
Agoraphobia								
15 x 3 min	TMS (iTBS)	N/A		Sham	PAS / HAMA/ CAQ	Change in PAS, HAMA, CAQ	No changes in symptoms	case study (follow-up)
Generalized anxiety disorder								
6 x 15 min	LF rTMS	N/A		No control	HRS-A / FADAS / HAMA	Change in HRS-A, FADAS, HAMA	Symptom improvement	RCT (double blind) unsuccessful blinding for patients
6 x 15 min	LF rTMS	N/A		No control	HAMA / PGI-T	Changes in HAMA, PGI-T	Symptom improvement	Open label design
24-36 x NR	Bilateral rTMS	N/A		No control	GAD-7 / HDRS-21	Change in GAD-7, HDRS-21	Symptom improvement	Open label study (6-month follow up)

(continued on next page)

Table 1 (continued)

#	Duration	NIBS type	polarity / electrode size	Control	Measure	Outcome	Outcome direction	Study type (blinding)
	30 x 15 min 30 x 15 min	LF rTMS LF rTMS	N/A N/A	Sham Sham	HRS-A / PSWQ/ CGI-S / CGI-IHRS-A / HRS-D / CGI-S / CGI-I	Change in HRS-A, PSWQ, CGI-I Change in HRS-A, CGI-I	Symptom improvement Symptom improvement	RCT 3-month follow up (double-blind) RCT 3-month follow up (double blind) unsuccessful blinding for experimenters RCT 1-month follow up (double blind) RCT 1-month follow up (double blind) RCT case study (45-day follow-up) RCT (single blind)
	25 x 20 min	HF rTMS	N/A	Sham	HRS-A / CGI	Change in HRS-A, CGI	Symptom improvement	
	10 x 36 min 30 x 15 min	LF rTMS LF rTMS	N/A N/A	Sham Sham	HRS-A / PSQI HARS, HADS, PSWQ	Change in HRS-A Changes in PSWQ		
	15 x 30 min	tDCS	cathodal F4-anodal left deltoid / 25 cm ²	No control	HARS / BAI / HRS	Change in HARS, BAI		
	15 x 30 min	tDCS	cathodal F4-anodal left deltoid / NR	Sham	HARS, PSWQ	Change in HARS, PSWQ		

Phobia Questionnaire (SPQ) (Olatunji et al., 2009). Moreover, they employed the Anxiety Sensitivity Index (ASI) (Reiss et al., 1986), the Questionnaire for the Assessment of Disgust Sensitivity (Disgust Scale; DS) (Haidt et al., 1994) and the Subjective Units of Discomfort Scale (SUDS) (Wolpe, 1973) for anxiety and disgust. They collected heart rate (HR) and electrodermal activity, which provide measures of autonomic nervous system activity (i.e., arousal) in the presence of fear-inducing stimuli. The authors reported no effects of iTBS on the self-reported measures of fear of spiders and anxiety. In contrast, an increase of HR in the iTBS group during observation of spiders, as compared to baseline, was found in the active group. No difference was reported in the sham group.

Herrmann et al. (2017) performed a double-blind, sham-controlled study to test whether 2 sessions of high frequency (10 Hz) rTMS over the medial prefrontal cortex (mPFC, coil positioned over FPz, according to the 10–20 EEG system) in 39 patients (average age 44.9, SD = 13.1) affected by acrophobia (fear of heights) boost the efficacy of virtual reality exposure-based therapy. For the assessment of symptoms, the Acrophobia Questionnaire (AQ) (Cohen, 1977) was applied. Moreover, the patients completed the Attitude towards Heights Questionnaire (ATHQ) (Abelson and Curtis, 1989), the State Trait Anxiety Inventory (STAI) (Spielberger, 1983), the Anxiety Sensitivity Index (ASI) (Deacon et al., 2003) and the Behavioral Avoidance Test (BAT) (McGlynn, 1988). The results showed that high-frequency rTMS improved the efficacy of virtual reality exposure-based therapy in these patients. For the AQ questionnaire, the reduction of anxiety was significantly higher in the active, compared to the sham group for both, anxiety and avoidance outcomes. A similar result was also shown for the BAT outcome. However, no significant difference between active and sham stimulation conditions was reported at follow-up (three months after the stimulation sessions).

With regard to tDCS research, Palm et al., 2018 have recently performed the first open-label pilot tDCS study on 8 patients (age range 24–59 years) affected by phobic postural vertigo (FPV) to modulate disease-related symptoms (vertigo/dizziness). 2 mA anodal tDCS was applied over the left DLPFC, one time per day for five consecutive days. For the assessment of symptoms, the authors used the Vertigo Symptom Scale (VSS) (Yardley et al., 1992), Dizziness Handicap Inventory (DHI) (Jacobson and Newman, 1990), and the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). Overall, the results show a significant reduction of DHI scores. Moreover, anxiety ratings were reported to be improved, but this result was not clinically significant.

In summary, the literature reviewed in this paragraph, although preliminary, suggests some beneficial effects of the application of excitatory non-invasive brain stimulation over the PFC in specific phobias. However, the heterogeneity of symptoms reviewed in this paragraph, the differences of the protocols (all reported studies refer to different stimulation protocols), the different cortical targets (left DLPFC vs. medial PFC), the different numbers of sessions (one vs. five) and the increased autonomic activity in response to the source of anxiety (i.e., spiders) in one of the three available studies preclude any definite conclusions about the preferable cortical target, and stimulation protocol.

3.2. Social anxiety disorder

According to the DSM-5 (Association, A.P., 2014) SAD is characterized by marked fear, anxiety or avoidance of social interactions, including situations in which one is scrutinized, or situations in which one is the focus of the attention (Craske et al., 2017).

The first rTMS study on SAD was conducted by Paes et al. (2013a) in a 38-year-old male patient (single case study). The patient was suffering from a specific SAD (writing in public), without comorbidities according to DSM-IV-TR. A single session of low frequency (1 Hz) rTMS was administered over the right ventromedial prefrontal cortex

(vmPFC). SAD was assessed by the Beck Anxiety Inventory (BAI) (Beck and Emery, 1985) and the Social Skills Inventory (SSI) (Riggio, 1986). Compared to pre-treatment, the BAI score was significantly reduced after intervention. At follow-up (2 months after the treatment) the patient still had reduced anxiety compared to pre-treatment, but showed a slight increase of anxiety as compared to the immediate post-treatment situation.

The same group of scientists (Paes et al., 2013b) performed another study on two patients (23 years old male, patient one; 45 years old female, patient 2) affected by SAD and comorbid depression. Both patients completed 12 sessions (3 per week for a total of 4 weeks) of low frequency (1 Hz) rTMS over the right vmPFC. SAD symptoms were assessed via BAI and the Liebowitz social anxiety scale (LSAS) (Liebowitz, 1987) at baseline (pre-treatment), 2 weeks, and 4 weeks after treatment initiation, and after 2 weeks of follow-up. For patient 1, the results reveal a significant reduction of LSAS and BAI scores. These improvements were also reported at the follow-up examination. Benefits were also reported for depressive symptoms, as obtained via the Beck Depression Inventory (Beck et al., 1961). A similar pattern of results was also reported for patient 2.

With regard to tDCS, Heeren et al. (2017) have recently performed a double-blind within-subject protocol in 19 female individuals with a DSM-5 diagnosis of SAD. Participants received a single session of anodal (2 mA) or sham tDCS over the left dlPFC during the completion of a probe discrimination task assessing Attentional Bias (AB). This task was chosen due to evidence that SAD is associated with and maintained by AB for social threat (Heeren et al., 2017). The results document a significant decrease in AB for threat during anodal tDCS over the left dlPFC relative to the respective sham stimulation condition.

Overall, the research presented in this paragraph provides preliminary evidence for an effect of right prefrontal inhibition/left excitation on social anxiety symptoms. No definite information regarding a preferable prefrontal sub-region is possible at this stage. This is also due to the heterogeneity of stimulation protocols, cortical targets (two of the three studies applied inhibitory stimulation over the right vmPFC, while the remaining study stimulated the left dlPFC with an excitatory protocol), the number of sessions (1 vs. 12 sessions), quality of respective studies, and heterogeneous outcome parameters (clinical vs surrogate). From a methodological point of view, the results provided by Heeren et al. (2017) might be considered the most reliable, as these were obtained by via a double-blind, sham controlled protocol, which provides an adequate control for placebo effects. However, this study has the limitation of having applied only a single stimulation session and examined social anxiety symptoms by a surrogate measure (i.e., attentional bias).

3.3. Panic disorder

According to the DSM-5 (Association, A.P., 2014), PD is classified as an anxiety disorder characterized by recurrent panic attacks with several potential symptoms such as palpitation, sweating, shaking, nausea, dizziness, derealization, and depersonalization.

The rTMS literature on PD provides a wide range of single case studies. Zwaninger et al. (2002) performed the first rTMS open case study in a 52-year-old woman who was treated with 10 sessions of low frequency (1 Hz) rTMS over the right dlPFC. PD symptoms were assessed via the Hamilton Anxiety Scale (HAS) (Hamilton, 1959), and Panic and Agoraphobia Scale (PAS) (Bandelow, 1999). After 2 weeks of treatment, the patient reported a significant improvement of her anxiety symptoms, as measured via HAS and PAS. Moreover, the authors report a significant reduction of cortisol levels associated to panic symptoms.

Guaiana et al. (2005) tested the effects of 9 sessions (3 times per week) of low frequency (1 Hz) rTMS over the right PFC (more details on this target region were not reported) of a 34-year-old woman. PD symptoms were assessed via the Panic Disorder Severity Scale (PDSS)

(Katherine Shear et al., 1997). This protocol did not result in clinically relevant effects. In contrast, left high-frequency (20 Hz) rTMS (20 sessions, three times per week) over the same region significantly improved PD symptoms in this patient.

A further case report study was conducted by Dresler et al. (2009). A 44-year old man affected by PD and comorbid depression was treated five times per week (one time per day) over a period of 3 weeks with high frequency (10 Hz) rTMS over the left dlPFC. To test therapeutic benefits of rTMS on PD, the patient performed an emotional Stroop task (Williams et al., 1996), in which 12 panic-related and 12 neutral words were displayed on a screen in one of three colours (red, blue, green). The patient had to indicate the color of the word by pressing a button on a standard computer keyboard as soon as possible. rTMS did not alter performance of this task. No significant reaction time differences were seen for panic-related and neutral words, when baseline values were compared with post rTMS outcomes. The authors, however, report that panic attacks did no longer occur during the course of the treatment, although mild anxiety was reported, which decreased in frequency and intensity during treatment. However, insufficient information is given on how panic symptoms have been monitored. The authors link their results to the possible influence of rTMS on panic-related prefrontal brain dysfunctions, as suggested by increased neural activity over this area shown via near-infrared spectroscopy after intervention.

A final single case study was performed by Machado et al. (2014). The authors tested one patient (age = 34 years old) affected by refractory PD and resistant to Cognitive Behavioral Therapy and drugs, by applying a combined rTMS protocol (3 times per week during 4 weeks) with a sequential stimulation of the right (low frequency, 1 Hz) and left (high frequency, 10 Hz) dlPFC. PD symptoms were assessed via the Beck Depression Inventory (Beck et al., 1961), BAI, PDSS and Clinical Global Impression – Improvement Scale (CGI-I) (Busner and Targum, 2007). The authors report a significant improvement of PD symptoms as evaluated via BAI and PDSS.

Mantovani et al. (2007) tested six patients (mean age = 50 years, SD = 18.46) affected by PD with depression comorbidity by applying low frequency (1-Hz) rTMS over the right dlPFC for 2 weeks in an open-label trial. Symptoms were monitored via the Sheehan Clinician Rated Anxiety Scale (SCRAS) (McGlynn, 1988), HAS and HDS, PDSS, BDI and Symptoms Check-List (SCL-90) (Holi et al., 1998). The patients showed significant reductions in SCRAS, HAS and HDS scores in the first and second weeks of treatment. Moreover, significant improvements were documented for PDSS, BDI, and Symptoms Check-List scores.

Prasko et al. (2007) tested fifteen patients affected by PD resistant to selective serotonin reuptake inhibitor (SSRI) therapy in a randomized, double-blinded - sham controlled study. The aim of the study was to explore the efficacy of 10 sessions of low frequency (1 Hz) rTMS applied over the right dlPFC in patients treated with SSRI therapy. Symptoms were evaluated via the PDSS (Katherine Shear et al., 1997), HAS (Hamilton, 1959), and BAI, two vs. four weeks after the treatment. The results show that both active and sham groups improved during the study period, but the treatment effect did not differ between groups in any of the instruments. This negative finding might be related to type second error (i.e., a false negative), caused by the small sample size (i.e., n 7 rTMS, n 8 sham stimulation), as suggested by the authors (Prasko et al., 2007).

Mantovani et al. (2013) performed a randomized, double-blinded, sham-controlled trial in 25 PD patients (mean age 40 years, SD = 11.6) with depression comorbidity. Patients were treated for 4 weeks (1 session per day over five consecutive days per week) by low frequency (1 Hz) rTMS over the right dlPFC. Clinical measures of anxiety symptoms included the PDSS and PDSS-self report. After 4 weeks of treatment, the response rate for panic symptoms was 50% with active rTMS, compared to 8% for sham rTMS. Significant improvements of both, PD and depression symptoms, were documented after 4 and 8 weeks of

treatment in the active stimulation sample. Clinical improvements were maintained at the 6-months follow-up.

A final open-label study has been performed by Kumar et al. (2018) in a group of 13 drug-resistant patients (age range: 28–52 years) affected by PD with depression comorbidity. The authors applied high frequency (20 Hz) rTMS over the left DLPFC for a total of 20 sessions (5 days per week over a period of 4 weeks). Symptoms were assessed via PDSS and HDRS. The results document a significant reduction of scores in both scales.

With regard to tDCS research, the literature reveals a case study by Shiozawa et al. (2014a). The authors treated a 44-year-old woman with 10 sessions (5 sessions per week, one per day, for 2 weeks) of cathodal (2 mA) stimulation over the right DLPFC (more details are reported in Table 1). The HAS showed a significant reduction of symptoms, as compared to baseline scores. Moreover, this pattern remained stable at the 30 days follow-up.

In summary, most studies reported here suggest potential beneficial effects of non-invasive brain stimulation over the DLPFC for the treatment of PD. Significant improvements were reported for inhibitory non-invasive brain stimulation over the right DLPFC and excitatory stimulation over the left DLPFC. Importantly, although most studies conducted were single case not sham-controlled, these results are consistent with those obtained in the randomized, double-blinded, sham-controlled study by Mantovani et al. (2013), suggesting that respective clinical improvements of the case studies might not be due to a placebo effect. On the other hand, the absence of clinically relevant results in the study of Prasko et al. (2007) suggests that further randomized, double-blind sham-controlled studies are required to come to clear conclusions about the therapeutic effectiveness of non-invasive brain stimulation for the treatment of PD. Moreover, it remains currently unclear whether the improvement of PD symptoms in patients with Depression comorbidity (Kumar et al., 2018; Mantovani et al., 2013; Sakkas et al., 2006) is linked to the improvement of depression rather than PD symptoms. Another source of variability is the heterogeneous number of stimulation sessions, which range from a minimum of 9 to a maximum of 40. The opposing outcome (i.e., no clinical effects in the study by Prasko et al. (2007) vs. relevant clinical effects in the study by Mantovani et al. (2013) in the two available double-blind, sham-controlled studies examined in this section might be due to the different amount of stimulation sessions. In the study by Mantovani et al. (2013), the authors applied 40 stimulation sessions, while only 10 stimulation sessions were applied in the study conducted by Prasko et al. (2007). Therefore, one might speculate that a sufficient number of stimulation sessions is critical for receiving clinical effects.

3.4. Agoraphobia

According to DSM-5 (Association, A.P., 2014), Agoraphobia is defined as an anxiety disorder characterized by marked fear or anxiety for situations such as public transportation, open or enclosed spaces.

Deppermann et al. (2017) have recently performed a functional infrared spectroscopy-controlled rTMS study in 44 patients (age range 18–65 years) affected by Panic Disorder (PD) with or without Agoraphobia. The patients were randomized to real or sham stimulation (double-blind design) and received 15 sessions of iTBS over the left DLPFC in addition to 9 weeks of group Cognitive Behavioral Therapy (CBT). Symptoms were measured via PAS (Bandelow, 1999), HAS and the Cardiac Anxiety Questionnaire (CAQ) (Eifert et al., 2000). Clinical ratings significantly improved during CBT and remained stable at follow-up. However, no clinical differences between the real- and sham-stimulated groups were identified, except for a more stable reduction of agoraphobic avoidance during follow-up in the real iTBS group. No studies in agoraphobic patients have been performed with tDCS so far.

With only one study available so far, which included also a relatively specific combined stimulation-psychotherapy protocol, available evidence is too preliminary to allow any definite conclusion with regard

to the effect of non-invasive brain stimulation for the treatment of agoraphobia.

3.5. Generalized anxiety disorder

Patients affected by GAD are characterized by persistent and excessive worries about a number of different things such as work, family, or money. Generalized anxiety disorder (GAD) is often associated with medical comorbidities (Hidalgo and Davidson, 2001), and is frequently chronic (Hidalgo and Sheehan, 2012).

Bystritsky et al. (2008) performed the first (not sham-controlled) open label pilot study to test the effect of rTMS on GAD symptoms. Ten participants with a DSM-IV diagnosis of GAD (age range between 18 and 56 years) completed 6 sessions of low frequency (1 Hz) rTMS over the right DLPFC over the course of 3 weeks. Symptoms were monitored via HAS (Hamilton, 1959). Overall, rTMS was associated with a significant decrease in HAS scores indicative for clinical improvement of GAD symptoms. Importantly, the clinical status remained improved compared to baseline over the 6 months between assessments (Bystritsky et al., 2009).

White and Tavakoli (2015) applied low frequency (1 Hz) rTMS over the right DLPFC followed by high frequency (10 Hz) rTMS over the left DLPFC in thirteen patients (mean age 42.46 years) affected by Depression and GAD. The number of treatments ranged from 24 to 36 over 5 to 6 weeks. Symptoms were assessed via the Generalized Anxiety Disorder (GAD-7) (Spitzer et al., 2006) and HDS (Hamilton, 1960) questionnaires. At the end of the treatment period, 11 out of 13 patients were in remission, as documented via GAD-7 and HDS.

Diefenbach et al. (2016b) performed the first randomized, double-blinded, sham-controlled trial for the treatment of GAD. Low frequency (1 Hz) rTMS (5 days per week for 6 weeks) was applied over the right DLPFC of 25 participants (14 active, 12 sham, mean age 44.29 years). Symptoms were assessed via HAS and the Penn State Worry Questionnaire (PSWQ) (Meyer et al., 1990). The results document a higher response rate to therapy in the active group, compared to the sham group. Importantly, these improvements maintained at the 3 months follow-up. Additional analyses published in a different article (Diefenbach et al., 2016a) indicate significant improvements in self-reported emotion regulation difficulties, as measured via the Difficulties in Emotion Regulation Scale (Gross and John, 2003), which also persisted at follow-up.

Dilkov et al. (2017) investigated high-frequency (20 Hz) rTMS applied to the right DLPFC in a randomized double-blind, sham-controlled trial of 6 weeks duration (25 rTMS sessions: 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) in 40 patients (age range 18–65 years) affected by GAD. Symptoms were assessed via HAS. The active (n = 15) treatment group showed a clinically significant reduction in HAS scores as compared to the sham (n = 25) group. Furthermore, at 2 and 4 weeks follow-up (after the end of treatment) HAS scores of the active group remained stable and even slightly improved.

The PFC was also the cortical target of a very recent randomized, sham controlled trial performed by Assaf et al. (2018). The authors applied low frequency (1 Hz) rTMS (30 sessions, 5 days/week for 6 weeks) over the right DLPFC in 16 patients (mean age 43.07) affected by GAD. The purpose of this treatment was to explore improvement in GAD symptoms in association with related brain connectivity changes. Worry symptoms were monitored via PSWQ and Intolerance of Uncertainty Scale (Freeston et al., 1994). Normalization of the functional connectivity of the dorsal anterior and subgenual cingulate (ACC) was associated with improvement in worry symptoms in the active, but not sham, stimulation group.

Finally, Huang et al. (2018) have recently performed a randomized, double-blind, sham-controlled pilot study in a sample of 36 patients (age range: 18–65 years old) affected by GAD and insomnia. The

authors applied low frequency (1 Hz) rTMS (10 consecutive sessions, 1 daily session) over the right parietal lobe (P4, according to the EEG 10–20 International system coordinates), with the purpose to target the attention network, which is involved in biasing attention towards threat (e.g., (Pergamin-Hight et al., 2015)). Symptoms were assessed via HAS and the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The active ($n = 18$) treatment group showed a clinically significant improvement of anxiety and insomnia symptoms, as documented via HAS and PSQI. Importantly, these benefits persisted over a 1-month follow-up period.

Shiozawa et al. (2014b) performed the first tDCS single case study in a 58-year-old woman affected by GAD. The authors performed 15 consecutive once-daily tDCS sessions (except for the weekends). The cathode was positioned over the right DLPFC, and the anode was placed extracephalic over the contralateral deltoid. Stimulation intensity was 2.0 mA, and tDCS was delivered once per day excluding the weekends. Anxiety symptoms measured via HAS and BAI significantly improved after 15 days of treatment. This improvement remained stable at follow-ups after 30 and 45 days.

In a more recent study (Movahed et al., 2018), a total of 18 patients affected by GAD (46% females and 64% males, mean age 28.7 (SD = 9.6)) were randomly assigned either to (2 mA) cathodal tDCS ($n = 6$) over the right DLPFC, pharmacotherapy ($n = 6$) or sham stimulation ($n = 6$). The authors adopted the protocol described by Shiozawa et al. (2014b). Symptoms were measured via HAS. The results show significant improvements of the anxiety index in the tDCS group, compared to the sham group.

In summary, the literature examined in this section suggests potentially long-term benefits of application of inhibitory (both rTMS and tDCS) non-invasive brain stimulation over the right DLPFC for the treatment of GAD. Moreover, inhibitory rTMS is therapeutically effective for the treatment of GAD also when applied to the right parietal cortex. The study of Dilkov et al. (2017) suggests that benefits on GAD symptoms might also be obtained by a treatment with high frequency (i.e., excitatory) rTMS over the right DLPFC. Future work in the field should aim to replicate this pattern, e.g. by use of anodal tDCS. Moreover, systematic investigations should be performed to clarify the ideal number of stimulation sessions and whether excitatory protocols over the left DLPFC might provide some benefit for the treatment of GAD, as already documented for PD.

4. Discussion

We systematically reviewed 27 published reports of studies in which non-invasive brain stimulation was administered to test effects on anxiety symptoms in patients affected by different anxiety disorders. Overall, the studies examined in this review support the concept that non-invasive brain stimulation represents a promising therapeutic approach for the treatment of anxiety disorders.

In most studies, an improvement of anxiety symptoms was associated with stimulation of the PFC, which represents the cortical target of 96% of the examined studies. In most cases, the cortical target was the DLPFC. The DLPFC is a relevant candidate target for the treatment of anxiety disorders via non-invasive brain stimulation, in line with suggestions (e.g., Liu et al., (2017)), and evidence (Banks et al., 2007) that its connectivity allows the modulation of the activity of several remote brain structures of the meso-cortico-limbic reward circuit - including the amygdala - which is known to be dysfunctional in anxiety disorders (See Duval et al., (2015) for a review). Tik et al. (2017) recently demonstrated that rTMS of left DLPFC modulates connectivity with the anterior cingulate cortex (ACC), which is part of a specific meso-cortico-limbic network typically associated with attention, mood and reward processing. In accordance, a previous study has shown that tDCS (e.g., Keeser et al., 2011) can induce changes in the neural activity/connectivity between the left DLPFC and the meso-cortico-limbic

network, including the ACC. This provides a physiological rationale that justifies the choice of the PFC as a neural target for non-invasive brain stimulation and might explain the therapeutic benefits reported in the studies mentioned here. With regard to DLPFC stimulation, it should be highlighted that our work suggests a precise relationship between the brain hemisphere (left or right) to be stimulated, and the type of stimulation (excitatory vs. inhibitory) to be administered. With the exception of one study (Dilkov et al., 2017), in which excitatory stimulation over the right DLPFC improved symptoms, clinical benefits were documented when applying excitatory stimulation over the left DLPFC and inhibitory stimulation over the right DLPFC. Nevertheless, current research in this field is not based on a detailed theoretical model that clarifies how stimulation of both hemispheres improves anxiety symptoms, as documented in our review.

Concepts about up-/downregulation properties of the DLPFC for emotional reactions might be helpful. Neuroimaging evidence suggests that the DLPFC is involved in emotion regulation (Davidson et al., 2000; see also Li et al., (2018)). In accordance, anodal (i.e., excitatory) tDCS over the left DLPFC may reduce the perceived degree of emotional valence for negative emotional pictures (Peña-Gómez et al., 2011), and for pictures of anger expressions (e.g., De Raedt et al., (2010)). Moreover, the left DLPFC may play a role in the upregulation of reactions to positive emotional stimuli, since anodal stimulation over this region improves the identification of positive emotional expressions (Nitsche et al., 2012a). On the other hand, the right DLPFC may be involved in the upregulation of negative emotional outcomes. High frequency (i.e., excitatory)- rTMS over the right DLPFC resulted in impaired attention disengagement from threat (angry faces) (De Raedt et al., 2010). A similar result has been documented by Leyman et al. (2009), showing that high-frequency rTMS over the right DLPFC can reduce the ability to inhibit the processing of negative information (sad faces).

Thus, stimulation of both the left and right DLPFC, might counteract maladaptive plasticity of the cortico-meso-limbic network in anxiety disorders by acting on the up-/downregulation mechanisms sub-served by these regions for emotional outcomes. Specifically, appropriate non-invasive brain stimulation protocols are assumed to work by upregulating positive reactions to positive emotional stimuli/outcomes, which are able to diminish the source of anxiety; and downregulating negative reactions to emotional stimuli/outcomes that underlie anxiety disorders. Both regulatory mechanisms (Fig. 2) might be prompted via excitatory stimulation of the left DLPFC, as this region is relevant for downregulation of negative emotion (e.g., Peña-Gómez et al., 2011) and upregulation of positive emotion (e.g., Nitsche et al., 2012b; Vanderhasselt et al., 2013). In addition, inhibitory stimulation of the right DLPFC might contribute to downregulate reactions to negative emotional stimuli/outcomes, as this cortical region is relevant for the upregulation (in terms of emotional control) of reactions to negative emotional outcomes (e.g., De Raedt et al., (2010)). According to the model discussed above, the amygdala represents the ultimate neural target that serves the up-/downregulation processes prompted by non-invasive brain stimulation.

To specifically test the up-/downregulation model discussed above, the exposure to positive/negative emotional stimuli/outcomes should be systematically included in non-invasive brain stimulation protocols of the left and the right DLPFC.

In this context, it might be relevant to consider also the vmPFC, a cortical structure explored only in 2 of the 27 studies examined in our review. An influential meta-analysis (Diekhof et al., 2011) has shown that the vmPFC of both hemispheres is involved in the down-regulation of negative affective responses and the degree of subjectively perceived unpleasantness (Diekhof et al., 2011). Importantly, this down-regulation of negative affect was accompanied by a concordant reduction of amygdala activation (Diekhof et al., 2011). Moreover, the vmPFC is relevant for the up-regulation for positive (rewarding) outcomes (Hutcherson et al., 2012). Therefore, the vmPFC is another key cortical

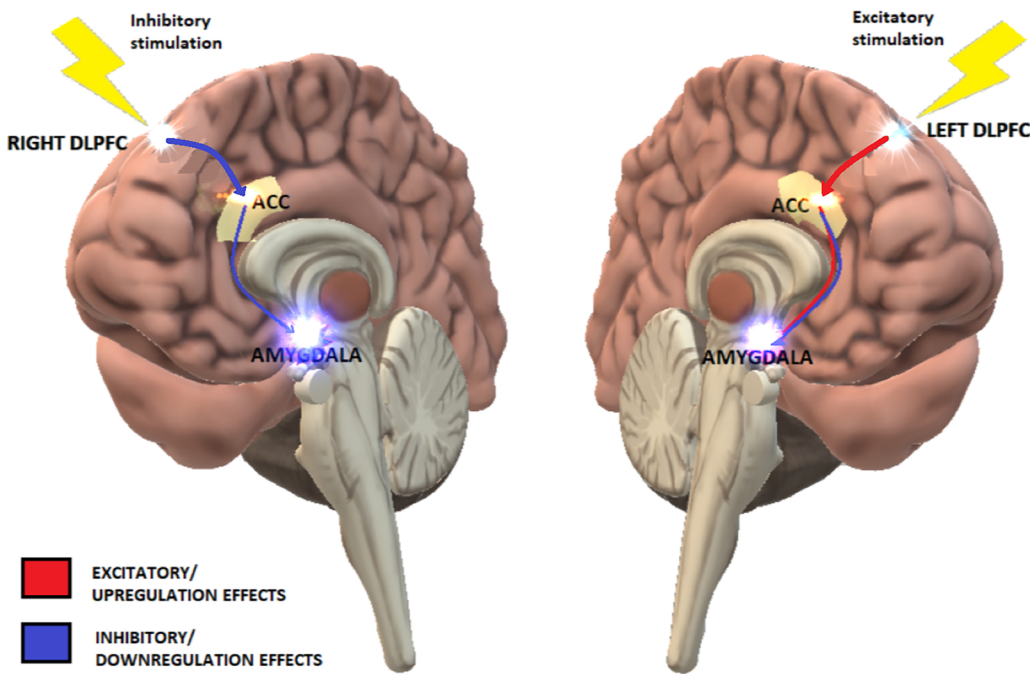


Fig. 2. Expected regulatory effects of non-invasive brain stimulation of the left and right DLPFC on the cortico-limbic pathway. Inhibitory stimulation of the right DLPFC might downregulate reactions to negative emotional stimuli/outcomes; excitatory stimulation of the left DLPFC might upregulate positive reactions to positive emotional stimuli/outcomes, and downregulate negative reactions to emotional stimuli/outcomes.

candidate to be systematically explored via non-invasive brain stimulation to test the up-/downregulation model for the treatment of anxiety disorders.

With regard to the examined anxiety disorders, PD and GAD were most frequently addressed in terms of single case and double-blind-sham controlled – studies, while Agoraphobia is the least well investigated clinical condition, with only one iTBS study. Therefore, the effect of non-invasive brain stimulation on Agoraphobia is currently a widely unexplored field (see the Fig. 3a for more details).

Another worthwhile aspect to mention is the relatively low number of tDCS studies. So far, 80% of the available studies used TMS. Therefore, more tDCS research is required to make any claim about the therapeutic effectiveness of this method for the treatment of anxiety disorders. With regard to the respective TMS studies, it is also important to note that 2 studies did not find clinically relevant effects on anxiety symptoms (i.e., Deppermann et al., 2017; Prasko et al., 2007). One of these was conducted with an iTBS protocol. Moreover, in the study by Notzon et al. (2015), iTBS even worsened the physiological response to anxious stimuli (i.e., spiders). Therefore, even if extremely limited, the currently available research conducted via iTBS (i.e., 2 studies) does not document clinical benefits for the treatment of anxiety disorders.

Although an improvement of symptoms has been associated with stimulation of both hemispheres, with both excitatory and inhibitory non-invasive brain stimulation, it is important to highlight that the majority of studies (about the 57.5%, i.e., 15 studies, Fig. 1b) conducted stimulation of the right hemisphere with inhibitory intervention protocols. On the other hand, only 23% (i.e., 6 studies) of the available studies targeted the left hemisphere via excitatory stimulation. This percentage is reduced to about 15% if we consider that two studies applied iTBS. Therefore, more work is required to substantiate the therapeutic effectiveness of excitatory stimulation protocols over the left hemisphere for the treatment of anxiety disorders. Among the remaining 5 studies, 2 were providing bilateral stimulation of the frontal lobe, with an inhibitory stimulation of the right hemisphere and excitatory stimulation of the left hemisphere; one study applied excitatory stimulation over a medial frontal region (FPz), one excitatory stimulation over the right hemisphere, and one excitatory stimulation over the right parietal cortex. For a detailed summary of the presented research please refer to Table 1.

In conclusion, our review documents promising, but yet

preliminary, evidence that non-invasive brain stimulation is an efficient tool for the treatment of anxiety disorders in adult populations. The main limitations of the available literature in the field, which should be addressed in future investigations, can be summarized as following: i) the high number of small and/or single case studies (i.e., about the 30% of the examined studies included 1 participant); ii) the low number of double blind, sham controlled studies (i.e., about 34% of the available studies); iii) the absence of systematic titration of stimulation parameters such as intensity, duration, repetition, and cortical target for optimization; iv) the absence of systematic protocols which combine non-invasive brain stimulation with standard therapies such as psychotherapy and/or pharmacotherapy; v) the absence of simultaneous exposure to emotional stimuli/outcomes to make use of up-/down-regulation properties of the DLPFC/vmPFC. Other relevant limitations of the current literature are the sole use of surrogate measures of anxiety disorders (in 2 of the 26 examined studies) instead of standard tests for anxiety symptoms, and difficulties to discern anxiety symptom reduction from depression symptom reduction in response to interventions, which would be relevant because depression is highly associated with many anxiety disorders (Kessler et al., 2015). Finally, respective limitations of the interpretability of open label trials should be taken into account, as they do not allow to exclude the relevance of placebo effects for the obtained effects.

4.1. Research perspectives in the field of anxiety disorders via non-invasive brain stimulation

For future studies in the field, some aspects are relevant to improve the impact of research regarding both mechanistic aspects of the intervention, but also the efficacy of respective interventions. Combination of clinical parameters with physiological measures, such as functional imaging, including fMRI, and EEG, and vegetative parameters (e.g., heart rate and skin conductance) associated with the disorder before and after treatment would be helpful. This would be useful for gaining information about biological mechanisms underlying successful/unsuccessful treatments via non-invasive brain stimulation, and thus **would** advance the field. Here, monitoring of neural network dynamics might be of specific relevance. This will provide a more comprehensive understanding of which cortical/subcortical dynamics lead to maladaptive neuroplasticity relevant for anxiety disorders.

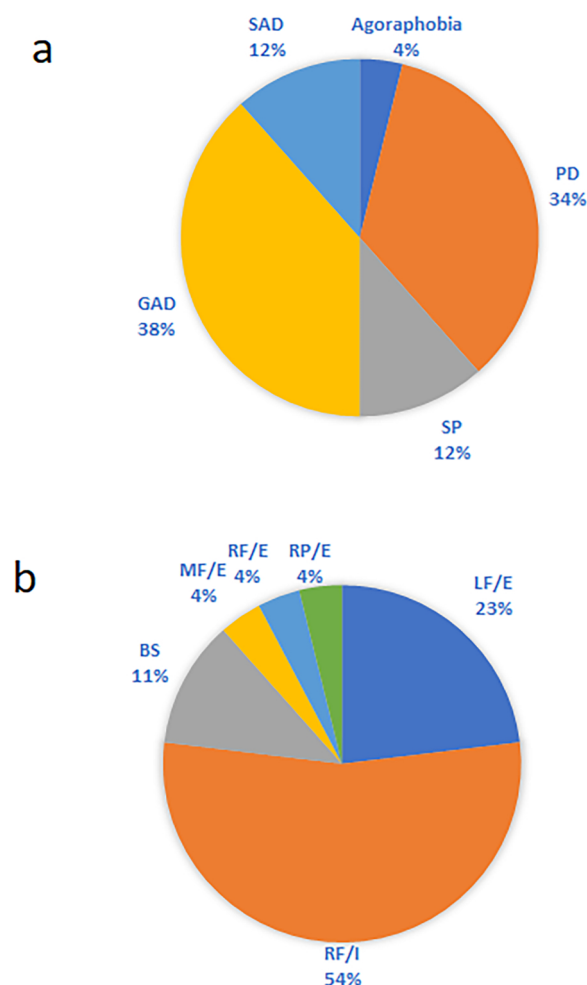


Fig. 3. a) Proportion of studies in the different Anxiety Disorders. PD (Panic disorder); GAD (Generalized anxiety disorder); SP (Specific phobia); SAD (Social anxiety disorder). b) The proportion of stimulation protocols. LF/E (left-frontal cortex/excitatory); RF/I (Right frontal/inhibitory); BS (Bilateral stimulation); MF/E (Medial-frontal cortex/excitatory); RF/E (Right frontal/excitatory); RP/E (Right parietal/excitatory).

These measures will deliver crucial information to optimize stimulation protocols in terms of cortical target, duration, frequency, and intensity of the stimulation approaches. It would be also useful to systematically evaluate the effects of non-invasive brain stimulation on patients under pharmacological and/or psychotherapeutic (including fear extinction protocols) treatments, to clarify how stimulation-induced neuromodulation can boost the efficiency of classical/consolidated therapies. In this regard, it might be also relevant to **develop** an individually tailored/personalized therapy approach that may allow to overcome the inter-individual variability frequently reported in response to the sole application of non-invasive brain stimulation (e.g., Muller-Dahlhaus et al., 2008).

Finally, it would be intriguing to widen the horizon of research in the field of anxiety disorder treatment to new non-invasive brain stimulation approaches such as transcranial focused ultrasound stimulation. Investigations on non-human primates (e.g., Mars et al., 2013) have shown that this method might be suited to modulate subcortical neural structures, which are critical for anxiety disorders, such as the ACC and the amygdala.

Declaration of interests

This work was supported by grants from the (i) Alexander von

Humboldt Foundation, Germany; ii) The SFB 1280 – Extinction learning; iii) The BMBF GCBS project (grant 01EE1403C). All authors declare no competing interests.

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