Noninvasive brain stimulation in combination with psychotherapy for anxiety disorders.

A systematic review

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Summary

Background: Although anxiety disorders can be treated very well with cognitive behavioral therapy, there are some patients who are not yet optimally benefiting from the therapy. In recent years, noninvasive brain stimulation methods have been studied as an add-on to psychotherapy.

Objectives. Is there sufficient evidence for the use of noninvasive brain stimulation in the psychotherapy of anxiety disorders?

Methods. A systematic review of previous therapy studies reviewing noninvasive brain stimulation in cognitive behavioral therapy of anxiety disorders.

Results. In total, only 4 randomized controlled therapeutic trials could be found and were analyzed. These studies used repetitive transcranial magnetic stimulation (rTMS) shortly before or during exposure-based behavioral therapy. The use of active stimulation compared to placebo stimulation shows a positive additional effect in the medium range.

Conclusions. Initial work shows an additional benefit of rTMS in cognitive behavioral therapy for the treatment of anxiety disorders. However, further studies must show which exact stimulation parameters are best suited to make a recommendation for the treatment practice

Keywords. Noninvasive brain stimulation, tDCS, rTMS, anxiety disorders, PTSD, phobia

Anxiety disorders represent a relevant group of mental illnesses that can be treated very well with cognitive behavioral therapy. In order to further optimize exposure therapy, non-invasive brain stimulation methods are currently being investigated in scientific studies to support specific psychological processes in the therapeutic approach. In this systematic review, we summarize all previous studies that investigate brain stimulation in conjunction with psychotherapy for anxiety disorders.

Introduction

Anxiety Disorders

More than 15% of the population suffer from an anxiety disorder at least once in their lives (Jacobi et al., 2014). This means that the frequency of anxiety disorders is even higher than that of affective disorders and disorders caused by substance abuse. Considering the global burden of disease, expressed as "disability-adjusted life years" (dalys), patients with anxiety disorders show the second highest burden of mental illness after patients with depressive disorders (Whiteford et al., 2013). Although cognitive behavioral therapy (CBT) is already very effective for anxiety disorders (Carpenter et al., 2018), not all patients benefit sufficiently from such treatment. For example, in the area of panic disorder, about 40% of patients did not show an

adequate response to therapy (Gloster et al., 2011). Further development of therapy methods is necessary and is being pursued in both large-scale multi-centre therapy studies (Arolt et al., 2009; Gloster et al., 2011) and also in experimental approaches (Shiban et al., 2017; Shiban et al., 2015). In addition, non-invasive brain stimulation procedures (NIBS) are being increasingly investigated as a complement to psychotherapy and psychopharmacological therapy (Bajbouj and Padberg, 2014; Zwanzger et al., 2016). The theoretical basis for this is provided, among other things, by imaging studies that have demonstrated changes in neuronal activation through psychotherapy (Brooks and Stein, 2015; Kircher et al., 2013; Lueken et al., 2013). From this, the question can be deduced whether additional modulation of these brain areas by suitable non-invasive brain stimulation procedures can achieve a positive therapeutic effect.

Non-invasive brain stimulation

Non-invasive brain stimulation procedures include transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). In TMS, a magnetic impulse is applied to the surface of the skull, which leads to an electrical current flow in the brain tissue and subsequently triggers depolarization of the neurons and action potential. The repetitive TMS (rTMS) is a repeated stimulation of cortical areas. This results in an inhibitory influence at slow (1 Hz) and an excitatory influence

at fast (from 5 Hz) stimulation frequency of the respective area (Lang and Siebner, 2007). In tDCS, a weak direct current is applied which flows between the anodal and cathodal electrodes. No action potentials are triggered, but a shift of the resting membrane potentials is caused. The anodal stimulation leads to a facilitated activation, the cathodic stimulation to a reduced activation (Nitsche and Paulus, 2000).

Two systematic reviews about the treatment of patients with panic disorder (Li et al., 2014) and post-traumatic stress disorder (Berlim and Van Den Eynde, 2014) by brain stimulation procedures show a positive effect of rTMS. However, the question of optimal stimulation localization, whether activating or inhibitory brain stimulation is more advantageous and, ultimately, whether and how a combination with psychotherapy makes sense remains open. Marin and colleagues (Marin et al., 2014) suggest that future studies should increasingly focus on therapy-relevant processes, such as fear extinction, which is an essential process in the exposure therapy of anxiety disorders (Vervliet et al., 2013). Initial studies have shown that both rTMS (Guhn et al., 2014; Raji et al., 2018) and tDCS (Dittert et al., 2018) can modulate fear extinction.

This systematic review integrates previous studies on the direct combination of brain stimulation procedures with psychotherapy for anxiety disorders.

Review

Search strategy

The systematic literature search included the databases Pubmed, CENTRAL, Web of Science, Ovid MEDLINE and PsychINFO and was carried out in October 2018 with the following search terms: (psychotherapy or "exposure therapy" or "add on" or augmentation or extinction) AND ("anxiety disorder" OR phobia OR GAS OR panic OR PTSD) AND (tdcs OR tms OR rtms OR NIBS). 223 references were identified, after removing duplicates 123

publications remained available for pre-selection (see flow chart in Figure 1). The pre-selection was carried out in parallel by two independent persons using the following inclusion and exclusion criteria:

Inclusion criteria:

- written in English or German language
- patients with diagnosed anxiety disorder were examined (ICD-10: F40, F41)
- psychotherapy was performed
- the study was carried out on humans
- only adult patients were enrolled

Exclusion criteria

- review, conference papers, commentary

13 papers were then tested for suitability in full text. Nine of the papers had to be excluded so that a total of four therapy studies could be included. One paper was written in Spanish, one paper did not include a control group, five papers did not include brain stimulation in a close temporal relationship to psychotherapy, and two other papers were to be evaluated only as feasibility studies, as these could only include up to five patients per therapy arm.

Results

Table 1 lists the studies included in this review. All papers use transcranial magnetic stimulation as a noninvasive brain stimulation method, with three papers using rTMS and one paper using a further development called deep TMS. In deep TMS, the coils for generating the magnetic field are attached in a complex form so that the stimulation effects can reach deeper brain areas as well (Zangen et al., 2005). Three of the studies examined patients with post-traumatic stress disorder (PTSD), one included patients with a specific phobia. Both for PTSD (Mühlberger and Voderholzer, 2015) and for a specific phobia (Bandelow et al., 2014) exposure-based therapy approaches are the procedure of choice, which in turn are partly based on extinction learning (Vervliet et al., 2013).

Table 1: Included studies

Author (year)	Diagnosis	N	f	Stimulation methods	localisation	duration	frequency
Osuch et al. (2009)	PTSD	17	0.21	rTMS	rDLPFC	20 x 30 minutes	100% MT 1 Hz
Isserles et al. (2013)	PTSD	26	*	deep TMS	mPFC	12 x 20 minutes	120% MT 20 Hz
Herrmann et al. (2017)	Phobia	39	0.38	rTMS	mPFC	2 x 20 minutes	100% MT 10 Hz
Kozel et al. (2018)	PTSD	103	0.31	rTMS	rDLPFC	12 x 30 minutes	110% MT 1 Hz

N= number of patients included; f = effect strength f for the interaction treatment group (verum, placebo) x time (pre-post); * not calculable due to data in the publication.
PTSD = post-traumatic stress disorder; rTMS = repetitive transcranial magnetic stimulation; rDLPFC= right dorsolateral prefrontal cortex; mPFC = medial prefrontal cortex; MT = motor threshold; Hz = frequency in Hertz

It is therefore obvious that the work of Isserles et al. (2013) and Herrmann et al. (2017) both define the medial prefrontal cortex (mPFC) as a target region since it plays an important role in extinction learning (Fullana et al., 2018). Both studies use repetitive TMS to activate the mPFC with the aim to augment the extinction learning during exposure therapy. In the first study (Isserles et al., 2013), a total of 26 patients with therapy-resistant PTSD were randomized to three therapy groups. One group received only rTMS (N = 8), one group received placebo stimulation (N = 9) and one group received rTMS in addition to the exposure sessions (N = 9). The exposure was based on an individualized audio script of approximately 30 seconds length. Exposure was performed in sensu for 20 minutes. A total of 12 sessions were completed in 4 weeks. The effect size in the group with exposure sessions and rTMS was $f=0.58$, in the rTMS only group $f=0.18$ and in the exposure session only group with placebo stimulation $f=0.16$. The study was performed as a randomized double-blind therapy study. Only the

user of the TMS knew which condition was applied, but not the patient or psychotherapist. 13% of the patients terminated the study prematurely, but there was no significant difference in the drop-out rate between the treatment groups. In the active stimulation group, one patient had a short, generalized seizure and the other reported side effects were minor (headache).

In the second study (Herrmann et al., 2017) two virtual reality exposure sessions were performed on 39 patients with height phobia. The exposure sessions (average duration 25 minutes), took place immediately after 20 minutes of rTMS or placebo rTMS. Similar to the first study, this study was conducted as a randomized double-blind therapy study in which only the user of TMS knew the condition. This study showed significant interactions between treatment group and time for both scales of the acrophobia symptom questionnaire AQ (Cohen, 1977). The effect size in the exposure group with placebo stimulation was $f=0.32$ for the scale "Anxiety" and $f=0.38$ for the scale "Avoidance". In the exposure

group combined with TMS, the effect size was $f=0.57$ for the "Anxiety" scale and $f=0.58$ for the "Avoidance" scale. For the interaction group x time, an effect size of $f = 0.38$ was found for the scale "Anxiety" and "Avoidance", respectively. The drop-out rate was only 7 % and was distributed equally across both treatment groups. The side effects reported in the active stimulation group were headache in 7 patients and drowsiness in one person. In the placebo-stimulated group, two patients reported neck pain and one person headache.

The other two studies (Kozel et al., 2018; Osuch et al., 2009) apply an inhibitory rTMS over the right DLPFC. Although the theoretical justification for this approach is not explicitly mentioned in the papers, the studies are based on preliminary results that have found a reduction of amygdala activity to threatening stimuli after 1 Hz rTMS of rDLPFC (Baeken et al., 2010). In the work of Kozel et al. (2018) with a total of 103 PTSD patients, an effect size of $f = 0.31$ was found for the significant interaction group x time (time 1 month after end of treatment) for the external assessment instrument CAPS (Blake et al., 1995). Here again, the decrease in symptoms was significantly stronger in the verum-stimulated group than in the placebo-stimulated group. The psychotherapeutic treatment included exposure sessions as well as cognitive elements and was performed in both groups once a week over a period of 12 weeks. TMS was performed for 30 minutes, followed by a

psychotherapeutic session for 60 minutes.

This study was a randomized double-blind therapy study as well in which only the user of the TMS knew the assignment to the stimulation conditions. The drop-out rate was 32% and was equally distributed across both groups. Headaches were reported as side effects in the active stimulation group of two patients and in the placebo stimulation group of one patient.

The next study, which combined psychotherapy with brain stimulation in the area of anxiety disorders, was published by Osuch et al. (2009). In this study, patients with chronic PTSD were treated with individualized gradual exposure therapy over 15 sessions. At the same time, patients received either an active or a placebo 1 Hz rTMS over the rDLPFC for 30 minutes. In total, only 9 patients in a crossover design were enrolled in the double-blind randomized study. One patient discontinued the study prematurely. No side effects were reported. The decrease of the hyperarousal subscale of CAPS was greater in the active TMS group than in the placebo-stimulated group with an effect size of $f = 0.21$. The reduction of the hyperarousal subscale of CAPS was greater in the active TMS group than in the placebo-stimulated group.

Discussion

In summary, it can be concluded that non-invasive brain stimulation can be well combined with psychotherapeutic procedures in the treatment of anxiety disorders. The mean, weighted effect

strength of such a procedure in comparison to a purely psychotherapeutic procedure with placebo stimulation lies with $f = 0.32$ in the range of a medium ($f = 0.25$) to large ($f = 0.40$) effect (Ellis, 2010). The discontinuation rate differs greatly between the studies and ranges from 7% to 32%. There are also clear differences between the studies in the area of side effects. In studies with rTMS applications, there is no difference between the verum- and placebo-stimulated groups. The side effects are in the range of mild headaches. The epileptic seizure that occurred with deep TMS can be considered a serious side effect. To what extent the activating stimulation of the medial PFC or the inhibitory stimulation of the rDLPFC will prove to be more effective will have to be investigated in future studies. The question of the extent to which medial PFC can be achieved with TMS cannot be answered in this review. Yet it is certain that deep TMS can reach deeper areas of the brain than standard TMS. It has also been shown that stimulation is not limited to the directly stimulated cortical area, but can reach deeper areas, such as the medial PFC, via functional coupling (Raij et al., 2018). Recent publications show that the tDCS method also improves extinction in healthy controls (Dittert et al., 2018) and can be combined with exposure procedures in PTSD (van 't Wout-Frank et al., 2019). Therefore, new randomized and controlled therapy studies will certainly be published with this method in the future. Furthermore, it is obvious to

augment exposure therapies for other anxiety disorders with non-invasive brain stimulation.

Conclusion for the practice

- Brain stimulation procedures for the augmentation of cognitive behavioral therapy in anxiety disorders are currently still in an experimental stage.
- Both basic studies on the modulation of fear extinction and first randomized controlled therapy studies show an additional benefit (mean weighted effect strength $f = 0.32$) of brain stimulation for exposure-based therapy in anxiety disorders.
- These initial positive results are encouraging, but additional randomized trials in various anxiety disorders must show which precise stimulation parameters are best suited to make a recommendation for treatment practice.

Conflict of interest. The authors state that there is no conflict of interest.

This article does not include primary data from studies on humans or animals.

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