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Medial prefrontal cortex stimulation accelerates therapy response of exposure therapy in acrophobia

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ABSTRACT

Background: Animal as well as human research indicated that the ventral medial prefrontal cortex (vmPFC) is highly relevant for fear extinction learning. Recently, we showed that targeting the vmPFC with high-frequency repetitive transcranial magnetic stimulation (rTMS) in a placebo-controlled study with 45 healthy controls induced higher prefrontal activity during extinction of conditioned stimuli (CS+) in the active compared to the sham stimulated group and better extinction learning as indicated by ratings, fear potentiated startles and skin conductance responses.
Objective: In this study, we aimed to proof our concept of accelerating extinction learning using rTMS of the mPFC in a group of anxiety disorder patients.
Methods: To specifically evaluate the impact of rTMS on exposure-based therapy, we applied a sham-controlled protocol over the vmPFC (FPz) succeeded by a virtual reality exposure therapy (VRET) in $n = 20$ participants with acrophobia and $n = 19$ controls.
Results: We found a significantly higher reduction in active compared to sham stimulated group for anxiety ($t[37] = 2.33$, $p < 0.05$) as well as avoidance ratings $t[37] = 2.34$, $p < 0.05$) from pre to post therapy.
Conclusion: This study provides first clinical evidence that high-frequency rTMS over the vmPFC improves exposure therapy response of acrophobia symptoms.

1. Introduction

Anxiety disorders constitute the largest group of mental disorders with a 12-month prevalence between 14.0% (EU [1]) and 18.1% (USA [2]). They are associated with a high individual and societal burden, e.g. in Europe total costs exceeded 70 billion € per year in 2010 [3]. Exposure-based cognitive-behavioral therapy (CBT) is a first-line treatment [4], but clinically significant change is only seen in approximately 50–65% of patients [5].

There is increasing evidence that - apart from psychopharmacologic and psychotherapeutic interventions - targeted modulation of neural networks by brain stimulation techniques might serve as a third treatment modality [6]. Vennewald and colleagues [7] reviewed the existing literature and suggested beneficial effects of repetitive transcranial magnetic stimulation (rTMS) on anxiety symptoms and neurocognitive functions [8,9] but argued that larger randomized controlled studies are warranted to allow a more comprehensive evaluation of the therapeutic efficacy of rTMS in anxiety disorders. Recently, two systematic reviews were published on this topic. Berlim and colleagues [10] summarized three controlled trials using rTMS in patients with post-traumatic stress disorder (PTSD) and Li and colleagues [11] analyzed two controlled trials on rTMS in panic disorder patients. Both reviews confirmed positive effects of rTMS, but the limited number of controlled trials restricts uniform recommendations about stimulation side or rTMS parameters. One problem of these studies might be that they used brain stimulation not to booster any learning in connection to specific processes. In contrast, Marin and colleagues [12] suggest focusing on a more mechanistic understanding of fear relevant processes to deepen our understanding of the pathophysiology of anxiety disorders. In detail they advised to search for ways to

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facilitate fear extinction learning because exposure therapy is likely based on these mechanisms [13].

Animal [14,15] as well as human [16,17] research indicated that the ventral medial prefrontal cortex (vmPFC) is highly relevant for fear extinction learning. Using functional near-infrared spectroscopy (fNIRS) we demonstrated that more superficial areas of the medial prefrontal cortex (mPFC) are also involved in extinction learning [18]. Targeting the mPFC with high frequency rTMS in a placebo-controlled study with 45 healthy controls [19] we revealed higher prefrontal activity during extinction of conditioned stimuli (CS+) in the active compared to the sham stimulated group and better extinction learning as indicated by ratings, fear potentiated startles and skin conductance responses. Thus, as suggested by Marin and colleagues [12] we found a way of enhancing fear extinction memory in the laboratory in a sample of healthy participants. The next important step is to extend this approach to a clinical sample as a first step to introduce these tools as potential adjuncts to augment the memory trace formed during exposure therapy and thus better treatment results.

Therefore in our present study we chose anxiety patients with a specific phobia as we aimed to proof our concept of accelerating extinction learning due to rTMS of the mPFC in a group of patients without medication and any serious psychiatric comorbidity. To allow a high level of control of the exposure procedure [20] we decided on a virtual reality exposure therapy (VRET). VRET is highly effective in specific phobia patients in general [21,22] and particularly in patients with acrophobia [23,24].

The aim of the present study therefore was to prove that high-frequency rTMS (10 Hz) improves the efficacy of exposure treatment of acrophobia. Based on the results of our previous study [19] we expect that, compared to a sham stimulated control group, the active stimulation group will show a greater reduction of phobic symptoms immediately after exposure sessions. To evaluate whether these effects persist over time, we will include a follow-up measurement after three months.

2. Materials and methods

2.1. Design

Participants meeting the inclusion criteria were randomly (simple randomization 1-1; controlling for the factor sex) assigned to two groups (active vs. sham). Participants and researchers conducting the exposure therapy were blind to the condition (double blind design). Participants gave written informed consent in accordance with the Declaration of Helsinki in its last version from 2013 [25]. All procedures were approved by the ethics committee of the University of Würzburg. The ClinicalTrials.gov Identifier is NCT02223767.

2.2. Measures

As a first primary outcome parameter “fear of heights” was evaluated using the German translation of the Acrophobia Questionnaire (AQ [26]). The AQ consists of two scales that assess fear (Anxiety) and avoidance behavior (Avoidance) ratings. Each of these scales comprises 20 items describing height situations (like standing on a chair, being in a Ferris wheel, or walking over a large bridge).

As a second primary outcome parameter we performed a Behavioral Avoidance Test (BAT). Accompanied by an experimenter patients walked to the flat roof of the six-story department building. The roof was about 10 m long and 5 m wide and on the opposite side of the door there was a grid-floor bridge that connected the roof to a grid-floor platform with a chimney. We instructed the participants to go as far as possible on a predefined course. The following approach scores were given: 0 = door to the roof remained closed, 1 = door is open, 2 = being on the flat roof 1 m behind the door, 3 = 5 m from the door, 4 = immediately in front of a bridge with grid flooring, 5 = on the bridge with grid flooring, and 6 = behind the bridge on a platform with grid flooring. At each point we asked the patients about their actual fear using the Subjective Units of Discomfort (SUD) ranging from 0 to 100. The participants were informed that the BAT was a measure of their fear of heights and not part of the treatment. During the test, the experimenter stayed behind the patient in order to minimize any potential impact of the experimenter's presence.

As mediating parameters we applied a German version of the Attitude Towards Heights Questionnaire (ATHQ [27]) to measure cognitive attitudes and risk evaluation and assessed the general anxiety levels with state and trait versions of the State-Trait Anxiety Inventory (STAI [28]), the anxiety sensitivity with the Anxiety Sensitivity Index-3 (ASI3 [29]), general positive and negative affective state (PANAS [30]) and depressive symptoms (ADS; Allgemeine Depressions Skala [31]). Additionally, we measured the duration of exposure sessions, the SUD ratings during exposure sessions and the presence ratings of the virtual reality experience (how much participants felt truly in the situation) as potential moderator variables.

2.3. Participants

Fifty one volunteers with self-reported heights phobia were recruited mainly through advertisements in local newspapers. The first screening was conducted via telephone; inclusion criteria were based on the DSM-IV criteria of specific phobia with following criteria: self-reported anxiety in height situations (at least 5 points on a scale from 0 to 10 [extreme anxiety]); the participant recognizes that the fear is excessive or unreasonable, height situations are avoided (at least 5 points on a scale from 0 to 10 [extreme avoidance]); the avoidance or the distress in the feared situations interferes significantly with the person's normal routine, occupational (or academic) functioning, or social activities or relationships. Additionally, the subjective motivation to do something about their fear had to be rated with at least 3 (on a scale from 0 to 10 [extreme motivated]) and the participants (with experiences with 3D movies) had to rate the amount of motion sickness below 4 (on a scale from 0 to 10). Exclusion criteria were previous treatment of their heights phobia within the last 6 months, metal parts in the head, medical implants, increased intracranial pressure, pregnancy, current involvement in psycho- or pharmacotherapy, and cardiovascular or neurological diseases. A family history of epilepsy and a history of tinnitus were also exclusion criteria. Forty-seven patients were randomized either to the verum group (active) or to the placebo control group (sham). After the first rTMS-exposure session two participants dropped out (one in each group), after the second rTMS-exposure session one participant additionally dropped out from active group. One participant from the sham group was excluded during data analysis due to extreme values (outlier with deviation more than three standard deviations). Additionally, we excluded 2 left handers each in the sham and active stimulation group.

In the final sample of N = 39 participants, gender (sham group: 6 males; active group: 7 males; $\chi^2 = 0.1$, $p = 0.82$) and highest school degree ($\chi^2 = 2.2$, $p = 0.54$) was equally distributed over active and sham group. In Table 1, age and rating scales for baseline measures are listed. With regard to mediating or moderating anxiety, depression and openness scales there was no consistent difference between active and sham treated patients.