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Intermittent theta burst stimulation of the left dorsolateral prefrontal cortex has no additional effect on the efficacy of virtual reality exposure therapy for acrophobia. A randomized double-blind placebo-controlled study

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ABSTRACT

Anxiety disorders are among the most common mental disorders. Treatment guidelines recommend pharmacotherapy and cognitive behavioral therapy as standard treatment. Although cognitive behavioral therapy is an effective therapeutic approach, not all patients benefit sufficiently from it. In recent years, non-invasive brain stimulation techniques, such as transcranial magnetic stimulation, have been investigated as promising adjuncts in the treatment of affective disorders. The aim of this study is to investigate whether a combination of intermittent theta burst stimulation (iTBS) and virtual reality exposure therapy leads to a significantly greater reduction in acrophobia than virtual reality exposure with sham stimulation. In this randomized double-blind placebo-controlled study, 43 participants with acrophobia received verum or sham iTBS over the left dorsolateral prefrontal cortex prior to two sessions of virtual reality exposure therapy. Stimulation of the left dorsolateral prefrontal cortex with iTBS was motivated by an experimental study showing a positive effect on extinction memory retention. Acrophobic symptoms were assessed using questionnaires and two behavioral approach tasks one week before, after treatment and six months after the second diagnostic session. The results showed that two sessions of virtual reality exposure therapy led to a significant reduction in acrophobic symptoms, with an overall remission rate of 79 %. However, there was no additional effect of iTBS of the left dorsolateral prefrontal cortex on the therapeutic effects. Further research is needed to determine how exactly a combination of transcranial magnetic stimulation and exposure therapy should be designed to enhance efficacy.

Abbreviations: ACRO, subscale anxiety of the Acrophobia Questionnaire; AD, anxiety disorders; ADS-K, Short form of the General Depression Scale; AQ, Acrophobia Questionnaire; ASI-3, Anxiety Sensitivity Index 3; ATHQ, Attitudes Toward Heights Questionnaire; AVOI, subscale avoidance of the Acrophobia Questionnaire; BAT, behavioral approach tasks; CAVE, Cave Automatic Virtual Environment; CBT, cognitive behavioral therapy; DIPS, Diagnostic Interview for Mental Disorders; dlPFC, dorsolateral prefrontal cortex; HIQ, Heights Interpretation Questionnaire; IPQ, Igroup Presence Questionnaire; iTBS, intermittent theta burst stimulation; ITQ, Immersive Tendencies Questionnaire; mPFC, medial prefrontal cortex; NIBS, non-invasive brain stimulation; PTSD, post-traumatic stress disorder; rTMS, repetitive transcranial magnetic stimulation; SSQ, Simulator Sickness Questionnaire; STAI-T, State-Trait Anxiety Inventory; SUD, Subjective Units of Discomfort Scale; TAS, Tellegen Absorption Scale; TMS, transcranial magnetic stimulation; vmPFC, ventromedial prefrontal cortex; VRET, virtual reality exposure therapy.

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1. Introduction

Anxiety disorders (AD) are among the most common mental disorders in the general population. Worldwide, the lifetime prevalence of total AD is about 17 %, with the highest lifetime prevalence for specific phobia at about 5 % [1]. Acrophobia in particular is one of the most common specific phobias with a lifetime prevalence at about 3–6 % [2]. AD lead to significant distress and impairments in patients' occupational and daily life [3] with a burden of disease of 24.6 million years lived with disability (YLD) in 2015 [4]. Furthermore, AD have the second highest value in terms of disability-adjusted life years (DALY) after depressive disorders [5]. With total annual costs of over 70 billion euros in 2010, AD are associated with a considerable socioeconomic burden [6]. In addition, AD have a high comorbidity with other mental disorders, which often leads to even more severe courses of disease [7]. The widespread prevalence of AD, frequent chronicity, and mental comorbidity as well as the associated psychosocial impairments and financial burdens emphasize the clinical and health policy importance of AD [8]. Therefore, effective and efficient treatment of AD is particularly relevant.

Pharmacotherapy and cognitive behavioral therapy (CBT), especially exposure therapy, are recommended as the standard of care for AD [9]. In the treatment of specific phobias, virtual reality exposure therapy (VRET) is recommended as an alternative when in-vivo exposure is not available or possible [9]. Numerous meta-analyses and systematic reviews showed that VRET is effective in the treatment of social phobia, agoraphobia and specific phobia and has comparable efficacy to in-vivo exposure (e.g., [10–14]). Additionally, VRET offers multiple advantages. A significant advantage is that VRET can reduce the rate of patients who refuse exposure therapy. Some patients refuse in-vivo exposure therapy because they are afraid of being confronted with real fear stimuli [15]. Another advantage is the possibility to choose different contexts for exposure sessions without leaving the treatment room. This is less time-consuming and more cost-effective [16]. The controllability of the stimuli and environmental variables by the therapist is another advantage. It is possible to adapt the stimuli individually to the needs of the patient [17]. Additionally, VRET allows to minimize possible confounding factors, such as weather, which is especially important for acrophobia.

Although CBT and hereby especially exposure therapy are effective therapeutic approaches, not all patients benefit sufficiently, and AD often return after remission [18,19]. A systematic review showed that only about 56 % of patients with AD remitted after CBT [20]. For this reason, it is necessary to optimize current treatment methods and to develop therapies that are more efficient.

In recent years, non-invasive brain stimulation (NIBS) techniques, such as transcranial magnetic stimulation (TMS), have been investigated as promising alternatives or complementary treatments to pharmacotherapy and CBT (e.g., [21,22]). In TMS, a magnetic field is generated in an isolated coil, which induces an electric current in the cortical tissue. The electric current activates superficial cortical neurons of a specific target region by triggering action potentials through a suprathreshold stimulus [23–25]. Repetitive TMS (rTMS) with a frequency below 1 Hz decreases cortical excitability and leads to an inhibitory effect. In contrast, rTMS with a frequency above 5 Hz increases cortical excitability and results in a stimulating effect [26]. Several systematic reviews showed a medium effect of rTMS as monotherapy for AD [22,27–32] as well as for other mental disorders [33,34] such as depression [35,36], obsessive-compulsive disorder [37,38], and post-traumatic stress disorder (PTSD) [25,27,39,40]. To further improve the efficacy of therapeutic approaches for AD, Marin et al. [25] argued to combine brain stimulation and exposure therapy in a way, that brain stimulation boosts relevant psychological learning mechanisms involved in exposure therapy such as fear extinction learning [41]. In line with these arguments, patients with AD exhibit deficits in the neuronal circuits, which are relevant for fear extinction [42]. A recent study by Pokorny et al. [43], for example, showed that patients with specific phobia exhibit reduced cortical inhibition in the dorsolateral prefrontal cortex (dlPFC). It was argued that the impaired prefrontal control results in abnormal activation of the amygdala [44]. Targeted stimulation of prefrontal cortex subregions using NIBS enables modulation within the affected dysfunctional neuronal circuits and can thus influence the processes of fear extinction. To achieve this goal, initial studies have examined how extinction learning can be modulated and enhanced by NIBS [45,46]. Some studies have already been published showing an augmentation effect of rTMS on exposure therapy in specific phobia (high frequency rTMS over the medial prefrontal cortex (mPFC) [47]) and PTSD (low frequency rTMS over the right dlPFC [48,49]), but additional research is necessary [50] to define optimal target location and dosing parameters.

One of the latest studies showing augmentation of fear extinction learning by NIBS was published by Deng et al. [51]. The authors showed a positive effect of an activating iTBS protocol of the left dlPFC on the retention of extinction memory after extinction learning in healthy controls. In detail, the laboratory study investigated 91 healthy participants using a three-day fear conditioning and extinction protocol. In this study, the authors applied iTBS over the left dlPFC before or after extinction training on the second day. The study has shown that iTBS, before as well as after fear extinction learning, resulted in enhanced extinction memory after 24 hours and one month compared to sham-iTBS. Based on the promising results of the study by Deng et al., this study aimed to translate this protocol [51] to a clinical trial in patients with AD. For this, we hypothesized that verum iTBS over the left dlPFC immediately before VRET leads to a significantly greater reduction in acrophobic symptoms compared to sham stimulation.

2. Material and methods

2.1. Study design

The present study is a randomized double-blind placebo-controlled study, with a baseline diagnostic session, two VRET sessions combined with preceding verum or sham iTBS, and two post-treatment sessions (one week after the last therapy session and six months after the second diagnostic session) for evaluation of the therapeutic and iTBS effects (see Fig. 1). The study procedure was adapted from our previous study [47], in which we investigated the effect of mPFC stimulation on treatment efficacy, so that the results can be directly compared. Both VRET sessions took place in a "Cave Automatic Virtual Environment" (CAVE). Participants were randomly assigned to either the verum or sham iTBS group before the first therapy session, stratified on sex. For randomization, a randomization list was created for both sexes using the block randomization method (block size 4), and participants were assigned to the next randomization code. The study was funded by the German Research Foundation and was approved by the Ethics Committee of the Medical Faculty of the University of Wuerzburg (proposal number 45/20). The study was conducted in accordance with Good Clinical Practice guidelines. Participants gave written informed consent in accordance with the Declaration of Helsinki and received €45 for their participation.

2.2. Participants

Inclusion criteria were as follows: 18–65 years of age, right-handed, and fluent in German language. The participants had also to fulfill the diagnostic criteria for specific phobia according to DSM-5 (situation: heights) based on self-reports (evaluated with the Diagnostic Interview for Mental Disorders (DIPS) interview guide) [52]. Exclusion criteria were as follows: neurological, cardiovascular, or other severe physical disorder; comorbid mental disorder (except for other specific phobias when acrophobia was the primary phobia; evaluated with the Diagnostic Short-Interview for Mental Disorders, MINI-DIPS [53]); pretreatment of

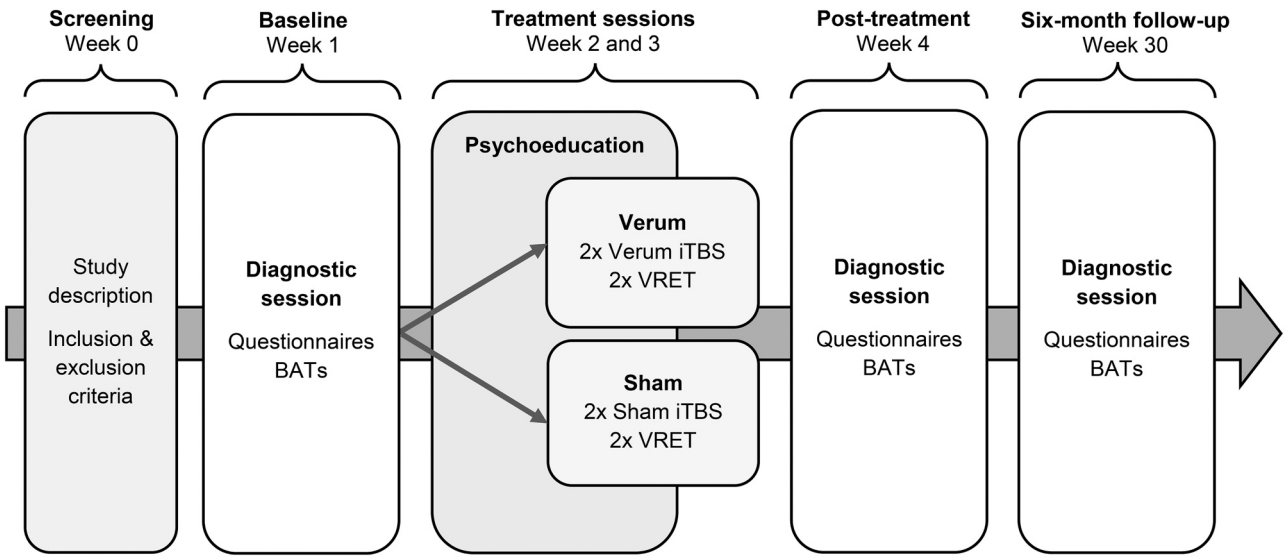

Fig. 1. Study design. Abbreviations: BAT, behavioral approach task; iTBS, intermittent theta-burst stimulation; VRET, virtual reality exposure therapy.

acrophobia; current psychotherapeutic or psychiatric treatment; use of tricyclic antidepressants, antipsychotics or other medications that increase cerebral seizure susceptibility; increased intracranial pressure; prior cranial injury or head surgery; epilepsy or a family history of epilepsy; non-removable metal (except the mouth; e.g., pacemaker, cochlear implant, infusion pump); and pregnancy. Calculating the sample size with two groups and a simple repeated-measures design with two measurements (interaction analysis pre-post * group) with an alpha below 5 %, a power of 80 %, and an effect size of $f = 0.3$ resulted in a sample size of $n = 46$ (based on one of our previous studies [47] and a systematic review [54]).

2.3. Study protocol

Participants were recruited mainly through public advertisements. During a telephone screening, the inclusion and exclusion criteria were provided and the study procedure was discussed. At baseline, after informed consent, a physical examination was conducted by a clinical physician, and demographic and psychometric data were collected using various questionnaires (listed in Section 2.6.1). In addition, behavioral data were collected using two behavioral approach tasks (BAT in VR and in-vivo). In preparation for the VRET, subjects received psychoeducational material on fear and the rationale for exposure therapy (based on a previous study [47]). Participants were instructed to read the material at home before the first treatment session. During the first therapy session, the psychoeducational material was discussed. Afterward, a short familiarization exercise was conducted to accustom the subjects to the VR and the technical conditions (e.g., controller, microphone). Before the two sessions of VRET, the participants received verum or sham iTBS to activate the left dlPFC. In addition, the subjects had to complete various questionnaires (listed in Section 2.6.1) during the therapy sessions. During post- and follow-up assessments, the same psychometric and behavioral data as at baseline were measured. During the post-treatment session, iTBS side effects were assessed. At follow-up, the diagnostic criteria for acrophobia were evaluated again using the DIPS interview guide [52], as an indicator of remission and the unblinding occurred after completion of the session.

2.4. iTBS and Beam-F3 system

Participants received iTBS immediately before both sessions of VRET. The stimulation localization of the left dlPFC corresponds to the F3 position of the 10–20 EEG system. For localization, the measurement method according to Beam et al. [55] was used. However, before performing iTBS, the individual resting motor threshold, defined as lowest stimulation intensity that induce visually observable finger twitches in at least five of ten TMS, was determined according to standard clinical practice [56] over the left motor cortex using a MagPro X100 stimulator and an MC-B70 coil (MagVenture GmbH, Willich, Germany). To match the MC-B70 coil to the Cool-B70 A/P coil (MagVenture GmbH, Willich, Germany), which was used for iTBS application, the distance of the MC-B70 coil to the head surface was increased by 2 mm with a plate attached to the coil, based on measurements of the induced magnetic field by MagVenture. The resting motor threshold was determined for each subject once during the first therapy session and used for both sessions.

For the double-blind iTBS application, the iTBS operator was instructed to turn the coil to one of the corresponding sides by entering a randomization code without being able to identify the condition. In the sham condition, no cortical tissue was stimulated, but the stimulation was accompanied by the same auditory artifacts [57]. For TMS before VRET, the iTBS protocol according to Huang et al. [58] was used. Three stimulation pulses with a frequency of 50 Hz were applied at intervals of 200 ms for two seconds. This was followed by a pause of eight seconds. During an iTBS session, which lasted 190 seconds, a total of 600 pulses were delivered. Following the study by Deng et al. [51], the stimulation was performed at an intensity of 80 % of the resting motor threshold. Simultaneously, in both iTBS conditions, superficial electrical co-stimulation of the scalp was performed at level 5 (control dial on the coil holder), which further made it difficult to distinguish between verum and sham conditions. For this, two 28 mm×20 mm surface electrodes (Ambu A/S, Ballerup, Denmark) were placed on the forehead. One electrode was placed vertically on Fpz and the second on the left at a 90° angle relative to the first electrode at a distance of 0.5 cm [57].

2.5. Virtual reality exposure therapy

Each participant received two sessions of VRET [47]. The VRET was conducted in the 3D multisensory laboratory of the Department of Psychology I at the University of Würzburg, Germany. For this purpose, a five-sided CAVE was available, which visually displayed the virtual environment. The CAVE has a size of 4 m x 3 m x 2.95 m. To generate the virtual environment, the VrExpoMod2 (VTplus, Würzburg, Germany) based on the Source Engine SDK 2013 (Valve, Bellevue, Washington, USA) was used in combination with the CS-Research 5.8 software (VTplus, Würzburg, Germany; for detailed information, see

www.cybersession.info). The virtual environment was projected onto the four walls and floor with six Galaxy NW-7 projectors (Barco GmbH, Kortrijk, Belgium) with a resolution of 1920 ×1200 pixels. For each projector, two computers rendered the images for the left and right eye respectively to create stereoscopic images. Passive interference-filtering glasses (Infitec Premium, Infitec GmbH, Ulm, Germany) were used for stereoscopic vision. A 7.1 surround system (Canton, Weilrod, Germany) was attached to the upper edge of the CAVE for auditory simulation (wind noises and birds chirping). The participants were able to navigate in the virtual environment with a gamepad (Xbox 360 Wireless Controller, Microsoft, Redmond, Washington, USA) and their movements in the CAVE. More technical details can also be found in previous publications (e.g., [59]). The fear-inducing scenario (developed by VTplus GmbH Würzburg, Germany) consisted of a tetrahedral observation tower with see-through metal grid stairs and four platforms located at about 18 m, 28 m, 35 m, and 50 m, with the highest platform only accessible by elevator.

During VRET, participants were instructed to walk up the observation tower as high as possible until they reached their maximum anxiety. In doing so, they were instructed to focus on their upcoming fear. On each platform, participants were asked about their anxiety using the Subjective Units of Discomfort Scale (SUD, scale from 0 % to 100 %; see 2.6.3). They should also approach the railing and report whether the fear changes in the process. If a participant reported anxiety < 100 % but had not yet reached the highest platform, they were instructed to continue ascending. When subjects reached their maximum anxiety level or the highest level of the observation tower, they were instructed to remain in place and focus on the appropriate fear stimulus while paying attention to changes in cognitive and physiological symptoms. The subjects were instructed to remain in the situation until habituation to anxiety (SUD rating $\leq$ 20 %) had occurred. During habituation, anxiety ratings were assessed every minute. Once habituation occurred, subjects were instructed to go back down the observation tower. VRET took place under therapeutic supervision to control safety and avoidance strategies. The therapist was able to communicate with the subjects via a microphone and monitor their behavior via two cameras. Following the VRET, a detailed debriefing was conducted.

2.6. Measurements

2.6.1. Questionnaires

2.6.1.1. Acrophobia questionnaire (AQ [60]). A self-report questionnaire that assesses the severity of acrophobia on the subscales of anxiety (ACRO) and avoidance (AVOI). Both subscales consist of 20 items that describe different height situations, such as “standing next to an open window on the third floor”. Each item of the subscale for ACRO is rated on a seven-point Likert scale ranging from 0 (“not anxious at all”) to 6 (“extremely anxious”), resulting in a sum score of 0–120. The items of the subscale for AVOI are rated on a three-point Likert scale from 1 (“would not avoid doing it”) to 3 (“would not do it under any circumstances”), resulting in a sum score of 20–60.

2.6.1.2. Attitudes toward heights questionnaire (ATHQ [61]). A self-report questionnaire that assesses feelings about height situations with six items. The items include pairs of dichotomous adjectives, such as “good/bad” or “safe/dangerous” and are rated on a scale from 0 (which corresponds to the first adjective) to 10 (which corresponds to the second adjective), resulting in a sum score of 0–60.

2.6.1.3. Heights interpretation questionnaire (HIQ [62]). A self-report questionnaire in which two different height situations (climbing a ladder and standing on a balcony) are presented with eight events (items) each, which are to be rated in terms of their probability of occurrence between 0 % ("will not occur") and 100 % ("will definitely occur"). These items include scenarios such as "they fall down" or "they are not able to bear their fear". The mean value (0–100 %) is calculated from all 16 items.

In addition to the acrophobia-specific questionnaires, the short form of the General Depression Scale (ADS-K [63]) to measure depressive symptoms, the Anxiety Sensitivity Index 3 (ASI-3 [64]) to measure the severity of various concerns related to anxiety symptoms, the State-Trait Anxiety Inventory (STAI-T [65]) to measure trait anxiety, the Tellegen Absorption Scale (TAS [66]) to measure hypnotic susceptibility, and the Immersive Tendencies Questionnaire (ITQ [67]) to measure the degree of immersion were used at baseline. During the first therapy session, the Simulator Sickness Questionnaire (SSQ [68]) was used after the exercise to measure simulator sickness, and the Igroup Presence Questionnaire (IPQ [69]) was used after both sessions of VRET to measure the sense of presence in VR. In addition, the STAI-S [65] was used before the BATs and two sessions of VRET to measure state anxiety.

2.6.2. Behavioral measurements

During the diagnostic sessions, the acrophobia and avoidance behavior were also measured on the behavioral level using two BATs in VR and in-vivo.

2.6.2.1. BAT in VR. The BAT was conducted with a VR Therapy System (VT+ExpoCart2, VTplus, Würzburg, Germany). The height scenario was developed by VTplus GmbH Würzburg, Germany. The participants were equipped with a VIVE Pro head-mounted display showing the virtual environment on a Dual AMOLED 3.5" diagonal screen with a resolution of 2880 ×1600 pixels for both eyes together. The subjects were able to control themselves in the virtual environment using a wireless controller (VIVE, HTC Corporation, 2018) and their movements. Participants were instructed to ride a glass elevator located on the outside of a skyscraper (50 floors) as high as possible without prolonged interruptions. Meanwhile, they were instructed to look down while going up and not to overcome their fear to avoid therapeutic effects. When subjects reached the 49th floor, they had the opportunity to enter the roof terrace (50th floor) and look down over the railing. During the BAT, the subjects were repeatedly asked to rate their anxiety using the SUD.

2.6.2.2. BAT in-vivo. Participants were instructed to walk up an open staircase with see-through metal grid stairs of a car park (four levels with a maximum height of 11.60 m) as high as possible without prolonged interruptions. Meanwhile, they were asked to look down while going up and were not supposed to overcome their fear. In addition, they were not allowed to hold on to the railing. On the respective levels, the subjects were repeatedly asked to rate their anxiety once when looking down through the transparent grid floor (center) and once when looking over the railing.

2.6.3. Ratings

During the BATs and VRET, the participants’ perceived anxiety was assessed using the SUDs ranging from 0 % ("no anxiety") to 100 % ("extremely high anxiety"). In addition, the individual feeling of presence in VR during the BATs and VRET was measured on a scale from 0 % (“not present at all”) to 100 % (“very present”).

2.7. Data analysis

Only subjects who participated in all study sessions were included in the data analysis. In total, $n = 43$ ($n = 20$ in the verum and $n = 23$ in the sham iTBS group) completed the study (see Fig. 2 for more details). SPSS 28 was used for the data analysis and $p < .050$ was set as the significance level.

The primary outcomes were the changes in the two subscales ACRO and AVOI of the height-specific questionnaire AQ from baseline to post-treatment. The changes from baseline to post-treatment and follow-up in

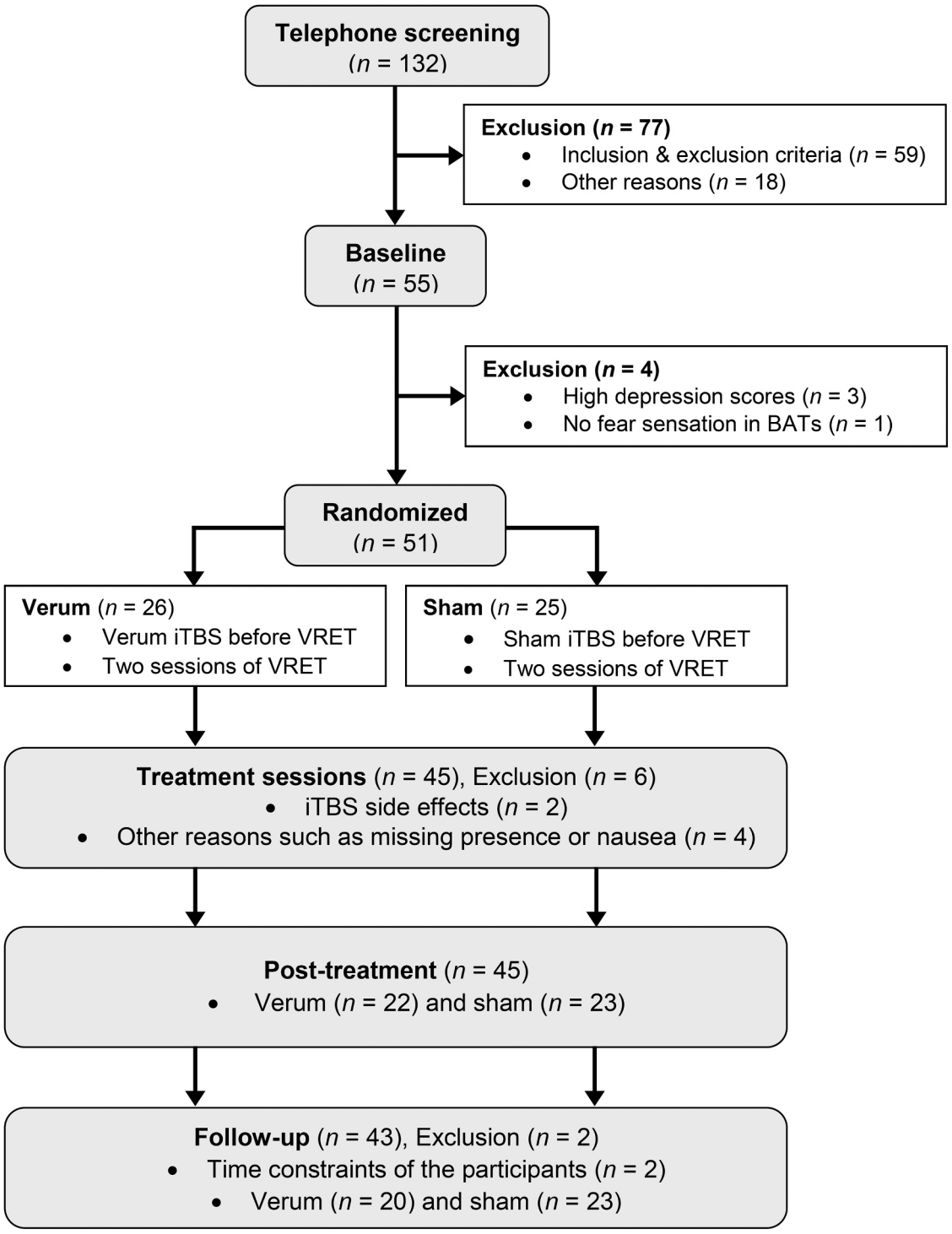

Fig. 2. Overview of included and excluded participants during the study. Abbreviations: BAT, behavioral approach task; iTBS, intermittent theta-burst stimulation; VRET, virtual reality exposure therapy.

ATHQ, HIQ, and STAI-S questionnaires (before the BATs), as well as in the behavioral parameters maximum perceived anxiety and maximum height at both BATs, represented the secondary outcomes. The follow-up data for ACRO and AVOI also served as secondary outcomes.

Group differences in demographic, psychometric, and behavioral data at baseline were tested with independent *t*-tests for continuous and chi^2-tests for categorical variables. Mixed-design ANOVAs were calculated with the within-subject factor time (baseline/post-treatment and baseline/follow-up) and the between-subject factor group (verum/sham iTBS). If there were significant effects, the changes from baseline to post-treatment or follow-up were further analyzed with an independent *t*-test for the differences between both groups. In addition, exploratory analyses were conducted to examine whether both groups differed regarding various exposure therapy characteristics (presence, minimum and maximum anxiety, maximum height, anxiety at the end of the habituation, exposure and habituation duration), the questionnaires SSQ, STAI-S and IPQ during the treatment sessions, as well as regarding iTBS characteristics (resting motor threshold and 80 %-intensity). For this purpose, both groups were compared in mean values and differences of the first and second exposure session using independent *t*-tests.

Furthermore, group differences regarding remission rate, iTBS side effects and blinding success (group expectancy) were examined using *chi²*-tests. Further exploratory analyses were based on previous studies [70,71] to investigate potential predictors of treatment response. We calculated multiple linear regressions with changes in the subscales ACRO and AVOI of the AQ for short- (baseline to post-treatment) and long-term (baseline to follow-up) treatment response. As independent variables we included personal variables (gender, age), baseline questionnaires (AQ, ADS-K, ASI-3, STAI), behavioral parameters (maximum height and anxiety in both BATs), exposure characteristics (maximum height and anxiety, duration), VR-specific variables (ITQ and TAS at baseline, IPQ and presence rating during exposure sessions) and iTBS specific parameters (group expectancy, real group). For the exposure characteristics and the VR-specific parameters IPQ and presence, the mean values and differences of the first and second exposure session were used for the analyses. We used the "*forward*" method to calculate the relevance of the predictors.

3. Results

3.1. Participants

We informed 132 persons about the study and the inclusion and exclusion criteria via telephone. Fifty-five participants were included in the study for the baseline assessment. Four participants had to be excluded during or after baseline due to increased depression symptoms load ($n = 3$; assessed with ADS-K [63]) or missing fear in the behavioral measurements ($n = 1$). The remaining participants were randomized into the verum ($n = 26$) and the sham group ($n = 25$). Six participants dropped out during or after the treatment sessions due to iTBS side effects (n = 2) and other reasons such as missing presence ($n = 1$) or nausea during the first VRET ($n = 1$), resulting in 45 participants at post-treatment assessment. For follow-up, two additional participants dropped out due to time constraints of the participants (remaining $n = 20$ in the verum and $n = 23$ in the sham group). Fig. 2 shows an overview of included and excluded participants during the study.

Table 1 provides a demographic and clinical description of the final sample ($n = 43$) in the baseline session. Participants in the verum iTBS group ($M = 40.9$, $SD = 15.5$) were significantly younger compared to the sham iTBS group ($M = 49.9$, $SD = 10.3$; $t(32.3) = 2.22$, $p = .033$). There are no other significant differences in anxiety and acrophobic symptoms (subjective and behavioral data), or in general affective or immersion and absorption parameters for VR (all p's $>.050$).

3.2. Primary outcomes

Both groups showed significant symptom reduction in primary outcomes from baseline to post-treatment assessment (see Table 2 and Fig. 3 for more details). We found a significant main effect *time* for the AQ subscale ACRO ($F(1,41) = 40.06$, $p < .001$, $\eta_p^2 = 0.50$) as well as for the AQ subscale AVOI ($F(1,41) = 64.90$, $p < .001$, $\eta_p^2 = 0.61$). However, no significant main effect *group* (ACRO: $F(1,41) = 0.00$, $p = .995$; AVOI: $F(1,41) = 0.27$, $p = .608$) and no significant *time x group* interaction (ACRO: $F(1,41) = 0.38$, $p = .543$; AVOI: $F(1,41) = 3.07$, $p = .087$) was found for both AQ subscales.

3.3. Secondary outcomes

For all secondary outcomes (see Tables 2 and 3 for more details), we found significant main effects of *time* (baseline to post-treatment or follow-up) with lower anxiety levels and increased heights (all p's $<.001$, except maximum anxiety in the BAT-VR from baseline to post-treatment: $p < .010$). The follow-up showed even lower mean scores for both AQ subscales (ACRO: $M_{verum} = 30.1$, SD = 17.9; $M_{sham} = 32.4$, $SD = 19.3$ and AVOI: $M_{verum} = 26.3$, $SD = 5.9$; $M_{sham} = 26.7$, $SD = 5.2$). For the maximum height in the BAT in-vivo from baseline to follow-up assessment ($n_{Verum} = 18$; $n_{Sham} = 22$), we found a significant main effect *group* ($F(1,38) = 4.29$, $p < .050$, $\eta_p^2 = 0.10$), but no significant *time x group* interaction ($F(1,38) = 0.07$, $p = .794$). The post-hoc tests for the changes between baseline and follow-up measurement showed no significant differences in the maximum height of BAT in-vivo between the verum iTBS group ($n = 18$, $M = 2.4$, $SD = 3.5$) compared to the sham iTBS group ($n = 22$, $M = 2.1$, $SD = 2.9$; $t(38) = -0.26$, $p = .794$). For all other secondary outcomes, we found no significant main effect of *group* and no significant interactions between *time x group* (all p's $>.050$).

At follow-up from $n = 45$, 14 % still fulfilled the diagnostic criteria for acrophobia according to DSM-5, 79 % no longer fulfilled them and 7 % were missing the values. The remission rate was not significantly different between the verum (85 %) and sham iTBS group (74 %; $\chi^2(1) = 2.29$, $p = .130$).

Table 1
Sample description at baseline assessment.

	Verum iTBS ($n = 20$) M (SD)/n (%)	Sham iTBS ($n = 23$) M (SD)/n (%)	Statistics t/chi^2	df	p
Female	14 (70 %)	14 (60.9 %)	0.39	1	.531
Age (years)	40.9 (15.5)	49.9 (10.3)	2.22	32.3	**.033**
Questionnaires					
ACRO	61.4 (14.9)	60.0 (18.8)	−0.27	41	.787
AVOI	35.6 (6.6)	35.1 (5.4)	−0.24	41	.814
ATHQ	40.6 (12.0)	36.6 (18.3)	−0.86	38.3	.397
HIQ	35.3 (17.3)	32.1 (14.5)	−0.67	41	.509
ADS-K	5.6 (3.8)	7.9 (5.9)	1.51	38.2	.140
ASI−3	13.0 (7.8)	18.5 (11.0)	1.87	41	.069
STAI-T	32.7 (6.9)	35.3 (9.2)	1.04	41	.304
TAS	51.2 (19.9)	46.1 (19.8)	−0.84	41	.405
ITQ	69.7 (14.2)	64.0 (10.1)	−1.54	41	.132
BAT (VR)					
STAI-S	41.1 (11.0)	39.1 (9.9)	−0.60	41	.551
Max. Anxiety	73.5 (19.0)	71.7 (25.2)	−0.25	41	.805
Max. Height	22.2 (20.6)	16.9 (18.1)	−0.90	41	.375
Presence	70.5 (25.6)	65.0 (27.4)	−0.68	41	.503
BAT (in-vivo)					
STAI-S	44.1 (12.4)	42.5 (11.5)	−0.44	41	.664
Max. Anxiety	67.5 (25.6)	63.8 (26.5)	−0.46	41	.652
Max. Height	9.1 (3.0)	7.7 (3.2)	−1.50	41	.141

Note: Test statistics for independent t-tests or chi², as appropriate, p <.050 (two-sided p-value). Displayed are the means and standard deviations; sum scores for the questionnaires (except HIQ: mean value in percent); anxiety and presence rating from 0 to 100 percent; BAT (VR) possible heights from 0 to 50 floors; BAT (in-vivo) possible heights from 0 to 11,60 m. Abbreviations: iTBS, intermittent theta burst stimulation; n, frequency; M, Mean; SD, Standard deviation; ACRO, anxiety and AVOI, avoidance subscale of the Acrophobia Questionnaire (AQ); ATHQ, Attitudes Towards Heights Questionnaire; HIQ, Heights Interpretation Questionnaire; ADS-K, German short form of the Center for Epidemiological Studies Depression Scale; ASI-3, Anxiety Sensitivity Index-3; STAI, State-Trait anxiety Inventory; TAS, Tellegen's Absorption Scale; ITQ, Immersive Tendencies Questionnaire; BAT, Behavioral Approach Task; VR, Virtual Reality; Max., maximum.

3.4. Exposure sessions effects

The mean duration of an exposure session was 27.3 minutes (range: 14–49 minutes; $n = 42$). On average, the participants stated a presence of 72.5 % (range: 15–100 %; $n = 42$) during a VRET. There was a significant difference between the two iTBS groups in terms of average presence during the two sessions of VRET ($t(40) = -2.25$, $p = .030$). The verum iTBS group ($M = 78.7$, $SD = 15.5$) reported a higher average presence during both sessions of VRET than the sham iTBS group ($n = 22$; $M = 66.6$, $SD = 18.3$). However, no significant difference was found in the change in presence from the first to the second VRET session between the two iTBS groups ($t(40) = -0.12$, $p = .902$). In addition, a significant difference was found between both iTBS groups with regard to the change in the IPQ subscale "Involvement" from the first to the second VRET session ($t(41) = 2.24$, $p = .031$). Otherwise, there are no

Table 2
Changes of primary and secondary outcomes from baseline to one-week post-treatment for both iTBS-groups.

	Verum iTBS *M* (*SD*)		Sham iTBS *M* (*SD*)		Statistics *F*			η_p^2
	Baseline	Post	Baseline	Post	Time	Group	T*G	Time
Questionnaires								
ACRO	61.4 (14.9)	45.6 (15.8)	60.0 (18.8)	47.0 (21.7)	**40.06*****	0.00	0.38	0.50
AVOI	35.6 (6.6)	28.5 (4.6)	35.1 (5.4)	30.6 (6.2)	**64.90*****	0.27	3.07	0.61
ATHQ	40.6 (12.0)	25.4 (8.5)	36.6 (18.3)	27.9 (11.7)	**38.42*****	0.04	2.83	0.48
HIQ	35.3 (17.3)	14.6 (8.8)	32.1 (14.5)	17.9 (16.7)	**63.90*****	0.00	2.21	0.61
BAT (VR)								
STAI-S	41.1 (11.0)	31.8 (7.5)	39.1 (9.9)	32.3 (8.6)	**20.80*****	0.10	0.47	0.34
Max. Anxiety	73.5 (19.0)	63.5 (25.6)	71.7 (25.2)	56.4 (31.2)	**8.78****	0.44	0.40	0.18
Max. Height	22.2 (20.6)	35.0 (17.1)	16.9 (18.1)	33.6 (20.6)	**34.77*****	0.40	0.59	0.46
BAT (in-vivo)								
STAI-S	44.2 (12.7)	32.2 (7.9)	42.5 (11.5)	31.1 (8.3)	**65.00*****	0.25	0.04	0.62
Max. Anxiety	67.8 (26.3)	53.2 (27.7)	63.8 (26.5)	41.4 (28.0)	**23.53*****	1.12	1.05	0.37
Max. Height	9.2 (3.1)	10.9 (2.4)	7.7 (3.2)	10.2 (2.7)	**33.50*****	1.86	0.86	0.46

Note: Test statistics for mixed-design ANOVAs. Displayed are the means and standard deviations; sum scores for the questionnaires (except HIQ: mean value in percent); anxiety rating from 0 to 100 percent; BAT (VR) possible heights from 0 to 50 floors; BAT (in-vivo) possible heights from 0 to 11,60 m. For F-values: ** p <.010, *** p <.001, df = 1,41 (except for all variables of the BAT in-vivo, df = 1,40). Missing values: n = 1 (Verum iTBS) for BAT in-vivo at post-treatment. Abbreviations: iTBS, intermittent theta burst stimulation; M, Mean; SD, Standard deviation; Post, Post-treatment; η_p^2, Partial eta-square; T*G, Interaction Time and Group; ACRO, anxiety and AVOI, avoidance subscale of the Acrophobia Questionnaire (AQ); ATHQ, Attitudes Towards Heights Questionnaire; HIQ, Heights Interpretation Questionnaire; BAT, Behavioral Approach Task; VR, Virtual Reality; STAI, State-Trait anxiety Inventory; Max., maximum.

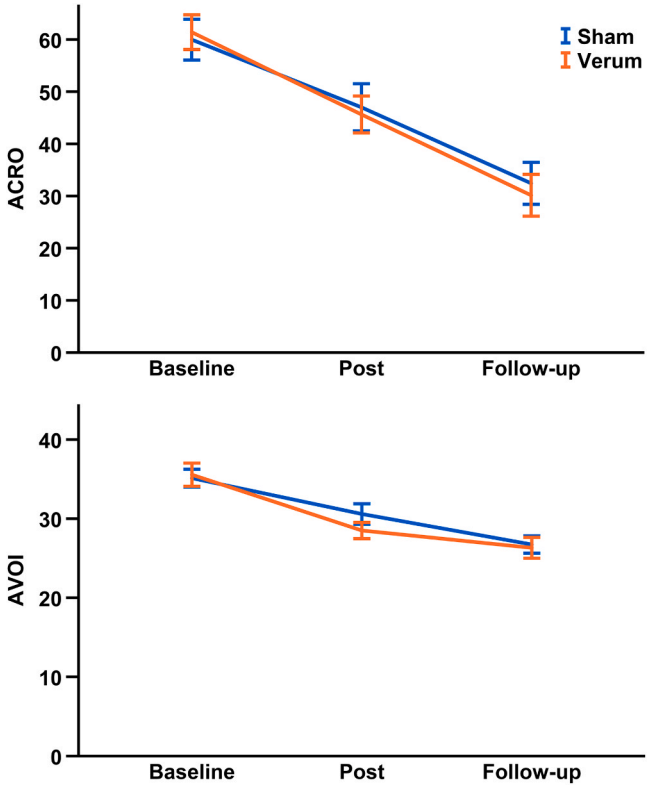

Fig. 3. Changes in the Acrophobia Questionnaire. Average change in mean scores (± standard error) for the Acrophobia Questionnaire (AQ) subscales "anxiety" (ACRO, range: 0–120) and "avoidance" (AVOI, range: 20–60) from baseline to post-treatment and follow-up for the verum and sham iTBS group. Time: p <.001.

significant differences for all other variables during the exposure sessions between both iTBS groups (all *p*'s >.050; see Table 4 for more details).

3.5. iTBS side effects and blinding

The 80 %-intensity of the resting motor threshold in the verum iTBS group was identical in both therapy sessions and was on average 28.8 (range: 21 – 39, see Table 4 for more details). Both the participants from the verum (50 %) and the sham group (26 %) reported iTBS side effects after the therapy sessions. No significant difference was observed between the two groups ($\chi^2(1) = 2.62$, $p = .106$). 50 % of the verum group and 74 % of the sham group did not report any side effects. No serious adverse events were reported during the study period. The following expected side effects occurred after the therapy sessions, which did not differ between the verum and sham group (all *p*'s >.050): headache (verum iTBS: 35.0 %; sham iTBS: 21.7 %), neck pain (verum iTBS: 15.0 %; sham iTBS: 4.3 %), dizziness (verum iTBS: 15.0 %; sham iTBS: 4.3 %), drowsiness (verum iTBS: 10.0 %), nausea (verum iTBS: 5.0 %; sham iTBS: 4.3 %), concentration disturbances (verum iTBS: 5.0 %; sham iTBS: 4.3 %), sleep disturbances (verum iTBS: 5.0 %; sham iTBS: 4.3 %). Symptoms reported only in single individuals are not listed here.

The blinding of the participants was successful. About 73.2 % of all participants ($n = 41$) suspected that they received iTBS (66.7 % of the verum and 78.3 % of the sham iTBS group; $\chi^2(1) = 0.69$, $p = .406$).

3.6. Predictors of treatment response

The multiple linear regression model ($n = 38$; see Table 5 for more details) with changes in ACRO from baseline to post-treatment (negative values indicate better improvement) showed that the expectancy of being in the verum iTBS group predicts a greater decrease in ACRO scores at post-treatment. In contrast, greater ITQ scores predict a lower reduction in the short-term outcome of ACRO. For changes in AVOI from baseline to post-treatment, we found that greater AVOI scores at baseline assessment, greater average exposure duration of the first and second exposure session, and the expectancy of being in the verum iTBS group predict a greater decrease in AVOI scores at post-treatment. Furthermore, a greater difference in presence between the first and second exposure session resulted in greater AVOI scores at post-treatment. The analyses for predictors of long-term treatment response showed, that greater ACRO scores and greater maximum height in BAT in-vivo at baseline-assessment predict greater reductions in ACRO scores at follow-up, as well as greater baseline AVOI scores predict greater reductions in AVOI scores.

4. Discussion

This double-blind placebo-controlled study examined for the first time the effect of iTBS over the left dlPFC on the efficacy of VRET in participants with acrophobia. For this purpose, 43 participants with

Table 3
Changes of secondary outcomes from baseline to six-month follow-up for both iTBS-groups.

	Verum iTBS *M* (*SD*)		**Sham iTBS** *M* (*SD*)		**Statistics** *F*			η_p^2
	Baseline	Follow-up	Baseline	Follow-up	Time	Group	T*G	Time
Questionnaires								
ACRO	61.4 (14.9)	30.1 (17.9)	60.0 (18.8)	32.4 (19.3)	**100.29*****	0.01	0.40	0.71
AVOI	35.6 (6.6)	26.3 (5.9)	35.1 (5.4)	26.7 (5.2)	**85.89*****	0.00	0.20	0.68
ATHQ	40.6 (12.0)	22.5 (14.9)	36.6 (18.3)	24.5 (9.3)	**41.68*****	0.08	1.63	0.50
HIQ	35.3 (17.3)	10.0 (10.9)	32.1 (14.5)	10.4 (9.6)	**70.71*****	0.22	0.43	0.63
BAT (VR)								
STAI-S	40.6 (11.5)	28.1 (4.7)	39.4 (10.1)	32.3 (7.5)	**30.78*****	0.44	2.35	0.45
Max. Anxiety	73.0 (18.5)	38.4 (23.8)	73.0 (25.1)	41.8 (27.5)	**56.73*****	0.07	0.15	0.60
Max. Height	23.4 (21.2)	36.7 (17.2)	17.6 (18.1)	33.4 (19.6)	**32.32*****	0.70	0.23	0.46
BAT (in-vivo)								
STAI-S	42.7 (11.0)	27.1 (4.5)	42.2 (11.7)	30.1 (8.0)	**58.06*****	0.29	0.91	0.61
Max. Anxiety	68.7 (23.3)	37.2 (28.3)	64.0 (27.1)	26.2 (25.9)	**69.37*****	1.18	0.59	0.65
Max. Height	9.4 (2.4)	11.8 (3.6)	7.9 (3.1)	10.0 (2.7)	**19.17*****	**4.29***	0.07	0.34

Note: Test statistics for mixed-design ANOVAs. Displayed are the means and standard deviations; sum scores for the questionnaires (except HIQ: mean value in percent); anxiety rating from 0 to 100 percent; BAT (VR) possible heights from 0 to 50 floors; BAT (in-vivo) possible heights from 0 to 11,60 m. For F-values: * p <.050, *** p <.001, df = 1,41 (except for all variables of the BAT-VR; maximum anxiety and height in the BAT in-vivo, df = 1,38; STAI-S in the BAT in-vivo, df = 1,37). Missing values: n = 1 (Sham iTBS) and n = 2 (Verum iTBS) for BAT-VR; n = 1 (Sham iTBS) for BAT in-vivo; n = 2 (Max. Anxiety and Height) and n = 3 (STAI-S) for BAT in-vivo in the Verum iTBS group. Abbreviations: iTBS, intermittent theta burst stimulation; M, Mean; SD, Standard deviation; η_p^2, Partial eta-square; T*G, Interaction Time and Group; ACRO, anxiety and AVOI, avoidance subscale of the Acrophobia Questionnaire (AQ); ATHQ, Attitudes Towards Heights Questionnaire; HIQ, Heights Interpretation Questionnaire; BAT, Behavioral Approach Task; VR, Virtual Reality; STAI, State-Trait anxiety Inventory; Max., maximum.

Table 4
Variables of intermittent theta burst stimulation and both sessions of virtual reality exposure therapy.

	Verum iTBS *M* (*SD*)		**Sham iTBS** *M* (*SD*)		**Statistics** *t* (*p*)	
	Mean	Difference	Mean	Difference	Mean	Difference
iTBS						
Resting motor threshold	36.0 (6.1)	-	35.8 (5.3)	-	−0.10 (.921)	-
80 %-Intensity	28.8 (4.8)	-	23.9 (22.4)	-	−0.96 (.345)	-
Exposure characteristics						
Presence	78.5 (15.5)	0.1 (11.4)	66.6 (18.3)	−0.6 (21.2)	−2.25 (**.030**)	−0.12 (.902)
Min. Anxiety	11.0 (6.2)	−1.1 (10.1)	9.7 (11.8)	−6.0 (10.0)	−0.42 (.677)	−1.58 (.121)
Max. Anxiety	95.6 (7.9)	−0.7 (5.1)	93.9 (11.1)	−7.4 (16.4)	−0.56 (.581)	−1.87 (.072)
Max. Height	6.6 (2.3)	0.2 (1.1)	5.7 (2.6)	1.1. (2.0)	−1.20 (.239)	1.95 (.059)
Anxiety (Habituation end)	18.6 (5.2)	1.1 (8.2)	17.6 (9.4)	−2.2 (11.4)	−0.43 (.669)	−1.05 (.300)
Exposure duration	28.3 (7.6)	−4.3 (5.9)	26.5 (5.7)	−2.1 (7.9)	−0.83 (.414)	0.97 (.340)
Habituation duration	9.1 (6.4)	−1.0 (3.2)	8.6 (6.2)	−1.1 (6.3)	−0.29 (.773)	−0.12 (.909)
Questionnaires						
SSQ (1st session)	31.2 (19.8)	-	28.5 (23.8)	-	−0.41 (.686)	-
STAI-S	39.4 (7.1)	−3.9 (9.2)	38.7 (9.0)	−5.0 (6.9)	−0.28 (.779)	−0.43 (.667)
IPQ (General Presence)	4.3 (1.2)	0.4 (0.9)	4.1 (1.4)	0.3 (1.0)	−0.59 (.557)	−0.01 (.994)
IPQ (Spatial Presence)	21.6 (4.5)	−0.4 (3.6)	20.8 (4.2)	−0.2 (3.9)	−0.56 (.576)	0.15 (.879)
IPQ (Involvement)	15.1 (3.8)	−0.4 (4.4)	13.6 (4.2)	2.6 (4.4)	−1.21 (.232)	2.24 (**.031**)
IPQ (Experienced Realism)	13.8 (4.3)	0.5 (3.8)	11.8 (4.9)	1.6 (2.7)	−1.39 (.171)	1.18 (.246)

Note: Test statistics for independent t-tests, as appropriate, p <.050 (two-sided p-value); df = 41 (except Presence = 40 and Exposure duration = 39). Displayed are the means and standard deviations for the mean value and difference of the first and second exposure session. Presence and anxiety rating from 0 to 100 percent; possible heights from 0 to 8; duration in minutes; sum scores for the questionnaires. Missing values: n = 1 (Sham iTBS) for Presence and n = 2 (Sham iTBS) for Exposure Duration. Abbreviations: iTBS, intermittent theta burst stimulation; M, Mean; SD, Standard deviation; Min., minimum; Max., maximum; SSQ, Simulator Sickness Questionnaire; STAI, State-Trait anxiety Inventory; IPQ, Igroup Presence Questionnaire.

acrophobia received verum or sham iTBS over the left dlPFC immediately before two sessions of VRET. The main finding of this study is that two sessions of VRET led to a significant reduction in acrophobic symptoms one week after treatment and six months after the second diagnostic session, measured with various questionnaires and behavioral data with high effect sizes (baseline-post effect sizes ranging from η_p^2 = 0.18–0.62). However, contrary to our hypotheses, no additional effect was observed in the verum iTBS group compared to the sham iTBS group.

The overall remission rate at follow-up was 79 %, which is quite high compared to other studies (46 % for example in a one-session VRET study in n = 186 patients with spider phobia [71]). Our analyses for the prediction of symptom reduction from baseline to follow-up does not reveal any specific aspects compared to other VRET studies. Krzystanek et al. [72] reviewed recent VRET studies with regard to the efficacy and reported that effectiveness of VRET in phobias is greater in patients without comorbidities, which might be an unspecific positive factor in our study. In particular, both iTBS groups showed high AQ anxiety scores (ACRO) at baseline, which were above the cut-off value of 45.45, indicating highly anxious and acrophobic subjects [62]. At follow-up, both groups achieved mean anxiety scores below this threshold, with scores similar to those observed in healthy individuals [62]. Our results support, comparable to previous studies, that VRET is effective in the treatment of patients with specific phobias and may represent an effective alternative to in-vivo exposure therapy [10,11,13,14].

One aim of the study, based on the laboratory study by Deng et al. [51], was to examine the feasibility of a combined treatment of TMS and subsequent VRET in a clinical setting with participants with acrophobia. Our study proves that two sessions of VRET, each preceded by iTBS, can be implemented in a clinical setting with subjects with acrophobia. An advantage of the methodical implementation of iTBS in this study is the shorter time required and the lower costs when determining the

Table 5
Predictors of short- and long-term treatment response.

	B	*SE*	β	*t*	*p*	R^2	cR^2	*F*	*p*
ACRO						0.32	0.28	8.32	.001
Group expectancy	−13.84	4.80	−0.40	−2.89	**.007**				
ITQ Baseline	0.47	0.18	0.37	2.65	**.012**				
Constant	−34.50	12.56		−2.75	**.009**				
AVOI						0.58	0.53	11.36	<.001
AVOI Baseline	−0.53	0.10	−0.64	−5.39	**<.001**				
Exposure duration (mean 1st/2nd)	−0.29	0.08	−0.42	−3.56	**.001**				
Group expectancy	−4.01	1.27	−0.37	−3.16	**.003**				
Presence (difference 1st/2nd)	0.08	0.03	0.30	2.46	**.019**				
Constant	23.82	4.56		5.23	**<.001**				
	B	*SE*	β	*t*	*p*	R^2	cR^2	*F*	*p*
ACRO						0.43	0.40	13.42	<.001
ACRO Baseline	−0.87	0.17	−0.78	−5.16	**<.001**				
Max. Height Baseline (BAT in-vivo)	−0.35	0.14	−0.37	−2.43	**.020**				
Constant	28.57	12.19		2.34	**.025**				
AVOI						0.42	0.41	26.42	<.001
AVOI Baseline	−0.69	0.13	−0.65	−5.14	**<.001**				
Constant	15.15	4.79		3.16	**.003**				

Note: Test statistics for multiple linear regression, as appropriate, p <.050. These analyses were performed for n = 38, as there are missing scores (n = 5); df = 37. Dependent variables: changes in the anxiety (ACRO) and avoidance (AVOI) subscale of the Acrophobia Questionnaire (AQ) from baseline to post-treatment and follow-up assessment. Independent variables: gender, age, group expectancy, real group; ACRO, anxiety and AVOI, avoidance subscale of the Acrophobia Questionnaire (AQ); ADS-K, German short form of the Center for Epidemiological Studies Depression Scale; ASI-3, Anxiety Sensitivity Index-3; STAI, State-Trait anxiety Inventory; TAS, Tellegen's Absorption Scale; ITQ, Immersive Tendencies Questionnaire (all questionnaires at baseline assessment); maximum height and anxiety at the Behavioral Approach Task in VR and in-vivo; mean value and difference of the first and second exposure session for presence, maximum height, exposure duration, maximum anxiety and IPQ, Igroup Presence Questionnaire General Presence. Abbreviations: SE, Standard error; ACRO, anxiety and AVOI, avoidance subscale of the Acrophobia Questionnaire (AQ), ITQ, Immersive Tendencies Questionnaire; Max., maximum; BAT, Behavioral Approach Task.

stimulation localization using the measurement method of the F3 position of the 10–20 EEG system according to Beam et al. [55] in comparison to more complex and longer-lasting neuronavigated localization techniques using structural MRI data. Nevertheless, it should not go unmentioned that the standardized Beam-F3 method may have led to a suboptimal targeting of the neural network to the clinical effect and it is important to find a balance between feasibility of implementation and individualization for optimization in future studies.

In line with some previous studies, we found no additional effect of iTBS over the left dlPFC on the efficacy of VRET for acrophobia. For example, Notzon et al. [73] showed in a virtual reality challenge study that a single iTBS over the left dlPFC does not reduce the subjective or psychophysiological fear responses of a 3 minutes challenge task. This is in line with our results, as we did not see any effects on subjective fear during exposure. A randomized clinical trial [74] applied 15 sessions of iTBS over the left dlPFC in addition to 9 weeks of group CBT did not find any beneficial effects compared to and sham-stimulated group regarding anxiety symptoms. However, both studies did not focus to modulate extinction-learning process as in our study.

We found in one of our previous studies, that facilitating rTMS over the mPFC (based on the laboratory findings of Guhn et al. [75]) before two sessions of VRET leads to significant improvement in anxiety and avoidance behaviour in participants with acrophobia [47]. This is in line with meta-analyses that have found hypoactivation especially of the ventromedial prefrontal cortex (vmPFC) during extinction learning and extinction memory recall [42,45], so it seems reasonable to further elaborate this target in further studies.

In another recent proof-of-concept study [76] no additional effect of iTBS over the vmPFC after in vivo exposure on the reduction of spider-phobic symptoms was found, but it was shown that a higher iTBS intensity led to a greater decrease in the subjective distress and skin conductance during BAT. Alternative stimulation sites should also be considered in further studies. Sydnor et al. [77] provide evidence that a TMS stimulation of the ventrolateral prefrontal cortex modulates the BOLD response of the amygdala and may be a candidate target for the treatment of AD.

One explanation for no TMS-effect could be that the high effectiveness of two sessions of VRET in phobic patients might have caused a potential ceiling effect. At least our descriptive data show that the verum iTBS group improved more from baseline to post-treatment than the sham iTBS group in all acrophobia specific questionnaires, although these were not significant differences. A possible reason for this result could be that the iTBS effects are too small. Based on the potential ceiling effect caused by the high effectiveness of two sessions of VRET in patients with specific phobia, further studies should include patients with more severe AD, where more exposure sessions are mandatory, like panic disorder. Another possibility for future studies could be the simultaneous use of TMS or another NIBS method, like transcranial direct current stimulation [78], during VRET in order to directly influence the learning processes during the exposure [79].

Since Deng et al. [51] showed a positive iTBS effect on the retention of extinction memory in healthy participants, our study underscores previous findings that highlight the challenges associated with transferring TMS effects from laboratory to clinical settings. On the one hand, the experimental learning designs are difficult to compare with one another. Healthy subjects in the laboratory often only need to view a stimulus on a computer screen compared to subjects interacting with a complex virtual reality during exposure therapy. Polanía et al. [80] describe that the NIBS effects vary depending on the experimental tasks. On the other hand, there are limitations in the direct transfer of conditioned fear memory mechanisms to the mechanisms observed in AD [81]. It is assumed that phobic disorders arise not only from an explicit aversive experience with a phobic stimulus, but also, for example, from the acquisition of fear via socially mediated information [82]. In addition, healthy subjects acquire a classic fear memory in laboratory studies over a very short period of time, which in turn is difficult to compare with a complex phobic memory in which additional neural mechanisms are involved and which has consolidated over a long time [83].

Another explanation of the missing translational effects between laboratory findings in healthy controls and clinical trials in patients with AD might be, that the functional brain activation of both groups differs concerning fear extinction processes [84]. Additionally, Chavanne et al. [85] showed in their meta-analyses that different AD show consistent but also different patterns of pathological functional activation. Therefore, it might be necessary to define the targets for NIBS on fear extinction in each AD separately.

Both TMS as monotherapy [22,27–32] and exposure therapy are effective for the treatment of AD. Therefore, the question is how exactly a combination of TMS and exposure therapy should be designed to show additional advantages. Marin et al. [25] argued to combine brain stimulation and exposure therapy in a way that brain stimulation boosts relevant psychological learning mechanisms involved in exposure therapy such as fear extinction learning [41]. However, future studies should look beyond fear extinction into other causal processes such as fear-memory reconsolidation [86]. For example, a fear conditioning study by Borgomaneri et al. [86] showed that rTMS over the dlPFC during the reconsolidation phase (10 minutes after fear reactivation) resulted in significant fear reduction 24 hours after stimulation compared with controls. Thus, the additional activation of the dlPFC using rTMS after fear reactivation in individuals with AD might provide an alternative approach to improve the efficacy of therapy. The results of this study emphasize, that it is important in future studies to investigate the exact timing of the combination of TMS and CBT. An alternative to our approach could be TMS following the exposure sessions [51,78].

The study by Deng et al. [51] showed positive rTMS effects 24 hours after stimulation. In translating these results into a clinical trial, it was important for us to focus not on short-term effects, but on therapeutically relevant periods, which is why we did the post-survey at one week and the follow-up at six months. The question of whether iTBS over the left dlPFC may have short-term beneficial effects cannot be answered with this design.

Regarding the predictors of treatment response (based on the studies of Leehr et al. [70] und Roesmann [71]), we found interesting results for the short-term reductions of acrophobic symptoms. Because we assessed whether participants believed they were in the verum or sham group only after therapy, it is possible that participants attributed a perceived therapeutic success to iTBS, and we therefore recorded less of a placebo effect. In future studies, we will record the expectation of group allocation both before and after therapy, in order to be able to consider both effects separately. Nevertheless it emphasizes the need for optimal blinding of participants and operators, e.g., by using a placebo TMS coil and corresponding electrical stimulation. Additionally, we found a negative effect of immersion (measured with the ITQ) and reduction in the mean scores of ACRO. Although previous studies have not found a direct effect of immersion on treatment outcome [87,88], our study showed that individual differences might cover small effects of TMS and should therefore be controlled in further studies investigating the effects of brain stimulation on VRET efficacy.

5. Conclusion

The present study provides valuable insight into the feasibility and efficacy of combining iTBS with VRET, although iTBS over the left dlPFC had no additional effect in the treatment of acrophobia. We showed that two sessions of VRET led to a significant reduction in acrophobic symptoms in the short- and long-term with an overall remission rate of 79 %. In the context of the highly effective approach used in this study, further research in clinical populations with more severe AD is needed. In addition to fear extinction, alternative anxiolytic mechanisms should also be taken into account.

Author statement

The manuscript “Intermittent theta burst stimulation of the left dorsolateral prefrontal cortex has no additional effect on the efficacy of virtual reality exposure therapy for acrophobia. A randomized double-blind placebo-controlled study" is not under consideration for publication elsewhere, and its publication is approved by all authors.

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CRediT authorship contribution statement

Paul Pauli: Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Thomas Polak:** Writing – review & editing, Investigation. **Martin Herrmann:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Barbara Bohmeier:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Lisa M. Cybinski:** Writing – review & editing, Supervision, Investigation, Data curation, Conceptualization. **Daniel Gromer:** Writing – review & editing, Methodology, Conceptualization. **Daniel Bellinger:** Writing – review & editing, Investigation. **Jürgen Deckert:** Writing – review & editing, Resources, Conceptualization. **Angelika Erhardt-Lehmann:** Writing – review & editing, Investigation, Conceptualization. **Lorenz Deserno:** Writing – review & editing, Supervision, Conceptualization. **Andreas Mühlberger:** Writing – review & editing, Supervision, Conceptualization.

Declaration of Competing Interest

PP and AM are shareholders in VTplus GmbH, a commercial company specializing in the development research systems for virtual environments. There are no other financial interests that could potentially compete with this agreement.

Data availability

Data will be made available on request.

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