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Neurobiological and clinical effects of fNIRS-controlled rTMS in patients with panic disorder/agoraphobia during cognitive-behavioural therapy

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ABSTRACT

Background: A relevant proportion of patients with panic disorder (PD) does not improve even though they receive state of the art treatment for anxiety disorders such as cognitive-behavioural therapy (CBT). At the same time, it is known, that from a neurobiological point of view, PD patients are often characterised by prefrontal hypoactivation. Intermittent Theta Burst Stimulation (iTBS) is a non-invasive type of neurostimulation which can modulate cortical activity and thus has the potential to normalise prefrontal hypoactivity found in PD. We therefore aimed at investigating the effects of iTBS as an innovative add-on to CBT in the treatment for PD.

Methods: In this double-blind, bicentric study, 44 PD patients, randomised to sham or verum stimulation, received 15 sessions of iTBS over the left prefrontal cortex (PFC) in addition to 9 weeks of group CBT. Cortical activity during a cognitive as well as an emotional (Emotional Stroop) paradigm was assessed both at baseline and post-iTBS treatment using functional near-infrared spectroscopy (fNIRS) and compared to healthy controls.

Results: In this manuscript we only report the results of the emotional paradigm; for the results of the cognitive paradigm please refer to Deppermann et al. (2014).

During the Emotional Stroop test, PD patients showed significantly reduced activation to panic-related compared to neutral stimuli for the left PFC at baseline. Bilateral prefrontal activation for panic-related stimuli significantly increased after verum iTBS only. Clinical ratings significantly improved during CBT and remained stable at follow-up. However, no clinical differences between the verum- and sham-stimulated group were identified, except for a more stable reduction of agoraphobic avoidance during follow-up in the verum iTBS group.

Limitations: Limitations include insufficient blinding, the missing control for possible state-dependent iTBS effects, and the timing of iTBS application during CBT.

Conclusion: Prefrontal hypoactivity in PD patients was normalised by add-on iTBS. Clinical improvement of anxiety symptoms was not affected by iTBS.

1. Introduction

With a 12-month prevalence of 2–3% (Kessler et al., 2006; Wittchen et al., 2011), panic disorder (PD) and comorbid agoraphobia represent a massively impairing anxiety disorder (Barlow, 2002) posing a substantial economic burden (Zaubler and Katon, 1998), and high

comorbidity and/or chronicity are frequently observed in this group of patients (Roy-Byrne et al., 2006). Fortunately, effective treatment options exist, as cognitive-behavioural therapy (CBT) has been proven effective in numerous randomised controlled studies (Bandelow et al., 2007; Hofmann and Smits, 2008; Schmidt and Keough, 2010). Moreover, pharmacotherapy has been confirmed to be beneficial in the treatment of PD with/without agoraphobia (Bandelow et al., 2008). However, up to one third of patients do not respond sufficiently to either approach (Diemer et al., 2010; Taylor et al., 2012). Several factors contributing to this phenomenon have been observed, e.g. disorder duration (Scheibe and Albus, 1996; Slaap and den Boer, 2001). Thus, despite a wide range of treatments available, improved therapeutic strategies for PD and agoraphobia are still needed.

From a neurobiological point of view of PD, alterations of the "fear network" in terms of hyperactivity of subcortical structures such as the amygdala have been consistently observed (cf. de Carvalho et al., 2010). Concurrently, a number of imaging studies have shown hypoactivation of the lateral prefrontal cortex, which is indirectly linked to the amygdala and is known to be critically involved in voluntary emotion regulation and cognitive control (Urry et al., 2006; Kent and Rauch, 2003; but see Dresler et al., 2013 for a comprehensive review). Since CBT works by changing problematic cognitions and prompting inhibitory learning (Craske et al., 2014), hypothetically, on a neurobiological basis, these effects of CBT should be associated with increased prefrontal activation which has in fact been shown in a number of studies (for a review see Clark and Beck, 2010). By implication, one could further conclude that directly enhancing prefrontal activation patterns in addition to CBT might enhance CBT outcome.

Based on the principle of electro-magnetic induction, repetitive Transcranial Magnetic Stimulation (rTMS) is capable of modulating cortical activity locally and non-invasively (Wassermann and Zimmermann, 2012). RTMS applied to the prefrontal cortex has been shown to exert antidepressant effects in several sham-controlled trials (Schutter, 2009; Berlim et al., 2013), however, inconsistent findings exist (Herwig et al., 2007). As a potential treatment option for anxiety disorders, the technique has so far been less investigated (Paes et al., 2011; Zwanzger et al., 2009). Although promising results have been demonstrated in small controlled trials, open studies and case reports (Mantovani et al., 2007; Paes et al., 2011; Zwanzger et al., 2009; Zwanzger et al., 2002; Dresler et al., 2009), again so far the findings are not conclusive and further controlled studies are needed to determine the optimal stimulation characteristics (Prasko et al., 2007) To increase cortical activity, the rTMS protocol intermittent Theta Burst Stimulation (iTBS) is recommended (Huang et al., 2005).

To evaluate cortical effects of neurobiological interventions, functional near-infrared spectroscopy (fNIRS) provides a non-invasive optical imaging technique that applies near-infrared light to measure task-related alterations of oxygenated and deoxygenated haemoglobin concentrations (Ferrari and Quaresima, 2012; Ehlis et al., 2014). Advantages compared to fMRI-investigations are considerable: fNIRS devices are mobile and allow for a more comfortable investigation without a potentially anxiety-inducing scanner environment, which might be particularly favourable for patients with claustrophobic difficulties (cf. Ohta et al., 2008).

In the present pilot study, we aimed at investigating, whether iTBS, applied concurrently to group CBT for PD, normalises prefrontal hypoactivity in terms of a "trans-situal characteristic" in this group of patients but also during specific fear-relevant situations. Do to so, we applied a cognitive task as well as an emotional task. Whereas the results of the cognitive task and the corresponding clinical data collected during the first three weeks of iTBS treatment have been published in Deppermann et al. (2014), this manuscript focuses on the results of the emotional paradigm (Emotional Stroop task) and the clinical data which was collected over the whole time course of CBT. More specifically, the following hypotheses were tested: (1) PD/agoraphobia patients are characterised by prefrontal hypoactivation, as assessed by

fNIRS, during a task that requires emotion regulation and cognitive control (Emotional Stroop task) compared to controls. (2) CBT and add-on iTBS normalises these activation patterns and (3) improves clinical symptoms. (4) Changes in fNIRS patterns are correlated with treatment efficacy.

2. Materials and methods

Inclusion criteria, implementation of fNIRS and iTBS application were identical to the procedures described in Deppermann et al. (2014) but, for more clarity, will be delineated again in the following sections.

2.1. Participants

The study included 44 patients, aged 18–65 years and diagnosed with PD with/without agoraphobia according to the DSM-IV-TR (American Psychiatric Association, 2000). PD with/without agoraphobia was diagnosed by experienced clinical psychologists with the Structured Clinical Interview for DSM-IV, Axis I Disorders (SCID-I; First et al., 1996; Wittchen et al., 1997). In the PD group, comorbid psychiatric disorders (except for bipolar or psychotic disorder, borderline personality disorder, acute substance abuse disorders and acute suicidality) were no exclusion criteria and the intake of psychopharmacological medication like selective serotonin (noradrenaline) reuptake inhibitors was permitted if the dosage had been kept stable for at least three weeks prior to baseline assessment.

23 healthy controls with no family history of mental disorders and no current or past mental, somatic or organic brain disorder were included. Groups did not differ with respect to gender, age, years of education, handedness, comorbid depression or duration of illness (Table 1). After a comprehensive study description, written informed consent was obtained. A clinical trial registration did not take place but the study was approved by the Ethics Committees of the Universities of Muenster and Tuebingen. All procedures were in accordance with the Declaration of Helsinki in its latest version.

2.2. Design

This multicentre study combined a 9-week CBT group intervention with a sham-controlled iTBS augmentation within the first 3 weeks of CBT. Patients diagnosed with PD with/without agoraphobia were randomised to either sham or verum iTBS. Enrolment took place between 01/2011 and 07/2013. Patients and therapists were blinded to iTBS group assignment (Fig. 1).

2.3. CBT

CBT (based on Margraf and Schneider (1990) and Schneider and Margraf (1998)) was conducted as a standardised treatment by trained clinical psychologists, who were continually supervised by experienced clinical psychotherapists. It was administered in a 9-week group setting (except for session 6) with a maximum of 6 patients/group. Two booster sessions took place after 3 and 6 months, respectively. Sessions lasted 1 ½ hours each, respectively (Fig. 1).

2.4. iTBS

After randomisation, a (sham) iTBS protocol (Huang et al., 2005) was applied over the left PFC in 15 daily sessions which always took place at the same time during the day for each individual patient but could vary between patients depending on their available free time during the first three weeks of CBT. We used a figure-of-eight coil (MCF-B65, 2×75 mm diameter, $n = 34$, MAGSTIM 9925-00, 2×70 mm, $n = 9$) using a MagOption/MagPro $\times 100$ stimulator (MagVenture, Denmark, $n = 35$), and a MAGSTIM RAPID2 T/N 3567-23-02 stimulator ($n = 9$), respectively. The rTMS coil was placed over electrode

Table 1
Baseline sample characteristics.

	Verum	Sham	Controls	Statistics	Post-hoc
Number in sample	22 (14)	22 (12)	23 (19)		
Mean age in years	37.6 (19–63)	36.3 (22–56)	33.4 (19–64)	$F_{2,66} = 0.807$, $p = 0.45$	
(range)	(38.4 (21–63))	(39.1 (24–56))	(34.7 (22–64))	($F_{2,44} = 0.74$, $p = 0.48$)	
% women	59 (50)	64 (75)	61 (63)	$X^2 = 0.097$, $p = 0.95$	
				($z = 1.70$, $p = 0.43$)	
Handedness (number of right-handed subjects)	20 (13)	21 (12)	20 (16)	$z = 1.037$, $p = 0.87$	
				($z = 1.89$, $p = 0.45$)	
First Language	19 (13) german	19 (11) german	22 (18) german	$z = 2.74$, $p = 0.64$	
	1 (0) bilingual	2 (1) bilingual	1(1) bilingual	($z = 5.73$, $p = 0.50$)	
	2 (1) other	1 (0) other	–		
Mean years of education	12.1 (1.7)	12.4 (2.0)	12.5 (1.1)	$F_{2,66} = 0.33$, $p = 0.72$	
(SD)	(12.2 (1.8))	(12.3 (2.4))	(12.4 (1.2))	($F_{2,44} = 0.033$, $p = 0.97$)	
Mean duration of illness in months (range)	92 (1–372)	84 (1–336)	–	$F_{1,43} = 0.084$, $p = 0.77$	
	(109.8 (18.372))	(111.2 (5–336))		($F_{1,25} = 0.001$, $p = 0.97$)	
Comorbid depression	8 (4) currently	6 (2) currently	–	$z = 0.56$, $p = 0.92$	
	9 (7) in past	11 (8) in past		($z = 0.86$, $p = 0.76$)	
	5 (3) never	5 (2) never			
Mean HAM-A – total (SD)	22.41 (8.97)	20.3 (7.1)	3.90 (3.35)	$F_{2,66} = 50.49$, $p < 0.001$	V = S > HC
	(21.14 (8.01))	(20.25 (8.66))	(0.26 (1.15))	($F_{2,44} = 33.45$, $p < 0.001$)	(V = S > HC)
Mean self-rated PAS total (SD)	20.76 (7.76)	20.52 (8.10)	0.22 (1.04)	$F_{2,66} = 75.64$, $p < 0.001$	V = S > HC
	(18.02 (7.92))	(18.83 (9.43))	(4.37 (3.24))	($F_{2,44} = 41.75$, $p < 0.001$)	(V = S > HC)
Mean CAQ – total (SD)	1.63 (0.71)	1.36 (0.51)	0.33 (0.20)	$F_{2,66} = 39.95$, $p < 0.001$	V = S > HC
	(1.52 (0.67))	(1.36 (0.54))	(0.32 (0.22))	($F_{2,44} = 29.49$, $p < 0.001$)	(V = S > HC)

CAQ: Cardiac Anxiety Questionnaire; HAM-A: Hamilton Anxiety Rating Scale; HC: healthy controls; PAS: Panic and Agoraphobia Scale;. S: sham group; SD: standard deviation; V: verum group; values in parentheses indicate results for the subgroup used for analyses of the behavioural data during the Emotional Stroop task. For all questionnaires, higher scores indicate higher severity of symptoms. For PAS, the median for PD-patients is reported to be 23 [Bandelow, 1997].

position F3 (left dorsolateral PFC) of the international 10–20 EEG system (Herwig et al., 2003). In order to adjust the stimulation intensity to the individual cortical excitability, the participants` resting motor threshold was defined prior to each iTBS application and stimulation intensity was set to 80% of it.

As a manipulation check, after all 15 iTBS sessions were completed, the participants were asked which stimulation (verum or sham) they believed they had received.

2.5. Outcome measures

2.5.1. Emotional Stroop task

The Emotional Stroop task consisted of 15 panic-related and 15 neutral words presented in red, green, yellow and blue. The words belonging to the two conditions did not differ significantly with regard to the number of letters, syllables and frequency in spoken/written language. Furthermore, they had already been used in prior studies (e.g., Dresler et al., 2012). Participants had to indicate the word colour independent of its meaning via button press. It is assumed that emotional, in contrast to neutral, words bind more attention due to

Screening	Screening patients: n = 312 / eligible to participate n = 72 / participation after informed consent: n = 63 / drop-outs: n = 19 (thereof n = 12 prior to treatment start; n = 6 during treatment)			
	Patients			*Healthy controls*
Baseline	Randomization fNIRS / HAM-A / PAS / CAQ (baseline)			fNIRS / HAM-A / PAS / CAQ (baseline)
		CBT	*ITBS*	
iTBS-7 (day 7)	HAM-A / PAS / CAQ	• S1: Psychoeducation • S2: Psychoeducation	*Active or sham stimulation*	
iTBS-14 (day 14)	HAM-A / PAS / CAQ	• S3: Psychoeducation		
Post-iTBS (day 21)	fNIRS / HAM-A / PAS / CAQ	• S4: Introduction exposure session		fNIRS / HAM-A / PAS / CAQ
		• S5: Preparing exposure session • S6: Exposure session (single – setting) • S7: Cognitive aspects of the vicious cycle • S8: Stress management		
Post-CBT	HAM-A / PAS / CAQ	• S9: Summary & relapse prevention		
Follow-up 1	HAM-A / PAS / CAQ (3 month) / booster session CBT			
Follow-up 2	HAM-A / PAS / CAQ (6 month) / booster session CBT			

Fig. 1. Study design.
Abbreviations: CAQ, Cardiac Anxiety Questionnaire; CBT, cognitive behavioural therapy; fNIRS, functional near-infrared spectroscopy; HAM-A, Hamilton Anxiety Rating Scale; iTBS, intermittent Theta Burst Stimulation; PAS, Panic and Agoraphobia Scale; S1-S9, therapy sessions 1 to 9.

emotional interference, thereby increasing reaction times (RTs) and error rates (ERs) for emotional words. For panic-related words, this effect should be more pronounced in PD patients (Dresler et al., 2012).

All 120 trials were presented in randomised order on a black LCD screen. A fixation cross (500 ms) preceded each stimulus (1500 ms), while the inter-trial intervals (4000–8000 ms) were randomly jittered.

We assessed RTs and ERs as indices of emotional interference.

2.5.2. fNIRS measures

FNIRS measurements were conducted using the ETG-4000 Optical Topography System (Hitachi Medical Co., Japan). The probe set consisted of 52 channels arranged in a 3×11 optode array (16 photodetectors and 17 light emitters). It was placed with its central optode of the lowest row on FPz stretching out towards T3 and T4, respectively, according to the 10–20 international EEG system (Jasper, 1958).

We recorded changes of the concentration of O_2Hb and HHb relative to the individual resting baseline during the Emotional Stroop task for the two conditions neutral words and panic-related words, respectively. The sampling frequency was set to 10 Hz. Measurements took place at baseline just before the beginning of the treatment period (within a range of 48 h before the first iTBS session) as well as after the completion of all 15 iTBS sessions. In order to avoid the measurement of acute iTBS effects, the post measurement was set to be performed after at least 12 h past the last iTBS session (please also refer to Fig. 1).

2.5.3. Clinical outcome measures

Quantitative psychometric assessment was administered at baseline, day 7 (iTBS-7), day 14 (iTBS-14), day 21 (post-iTBS), the end of CBT (post-CBT, week 9), and at 3-month and 6-month follow-up after CBT (Fig. 1). The following questionnaires were used:

The Panic and Agoraphobia Scale (PAS; Bandelow, 1997) consists of an observer-rated and a self-rated questionnaire assessing symptoms of PD with or without agoraphobia with reasonable reliability and validity (Bandelow, 1997). Each item scores from 0 to 4, with higher scores indicating higher symptom severity. We assessed the total score indicating global severity on both the observer-rated and the self-rated questionnaires, as well as 5 subscores per questionnaire: a) panic attacks, b) agoraphobic avoidance, c) anticipatory anxiety, d) disability and e) worries about health (Bandelow, 1997).

The Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1996) is an observer-based, clinical interview assessing a comprehensive range of anxiety symptoms. Beside a total score, the subscales "somatic anxiety" and "psychic anxiety" can be calculated. Higher scores indicate a stronger severity.

The Cardiac Anxiety Questionnaire (CAQ; Eifert et al., 2000; Hoyer et al., 2005) is a self-report questionnaire with good reliability and validity, designed to assess heart focused anxiety (Eifert et al., 2000;

Hoyer et al., 2005). Each item scores from 0 to 4 with higher scores indicating stronger symptoms. Beside a total score, 3 subscales (fear, avoidance, attention) can be calculated.

2.6. Data preparation

Matlab was used to correct for fNIRS signal changes that were not directly due to functional changes in haemoglobin concentration related to the attended tasks and included the following steps: the data was filtered with a high pass of 0.03 and a low pass of 0.5 Hz, manual interpolation of channels which clearly displayed technical artefacts according to a Gaussian distribution (circumjacent channels were taken more into account), a correlation-based signal improvement (CBSI) procedure according to Cui et al. (2010), automatic Gaussian interpolation for channels where the within-subject variance exceeded four. Due to technical problems, complete data sets were only available from $n = 20$ verum-stimulated patients, $n = 21$ sham-stimulated patients, and $n = 21$ healthy controls. The data of the remaining participants were segmented channel-wise in an event-related manner. A time frame of 0–16 s after stimulus onset was extracted and adjusted for linear drifts and baseline. The resulting averaged amplitude integrals (4–10 s after stimulus onset) were taken as the basis for statistical analyses.

For the data of the clinical assessment (HAM-A, PAS, CAQ), a last observation carried forward analysis (LOCF) was applied, if drop-outs or complete omissions of questionnaires between any times of measurement occurred. If there were questionnaire items missing, missing values (if $< 10\%$) were substituted by the mean value of the subject on the relevant scale.

2.7. Regions of interest (ROI)

To assess the effects of the stimulus-related oxygenation changes as well as iTBS treatment, regions of interest (ROIs) were defined a priori. This was done in agreement with current findings on Emotional Stroop paradigms which are known to activate prefrontal areas (such as our site of iTBS application) as the major neural correlate of cognitive control (Tupak et al., 2013; Zhang et al., 2011; Dresler et al., 2012). The channels, including the left and right PFC ROIs, were chosen with respect to a virtual registration procedure described by Tsuzuki et al. (2007), Singh et al. (2005), Rorden and Brett (2000) and Lancaster et al. (2000) (Fig. 2). In order to additionally verify that the expected activation changes were unique to the predefined ROIs, a control "non-ROI" comprising all temporal channels was defined.

2.8. Statistical analyses

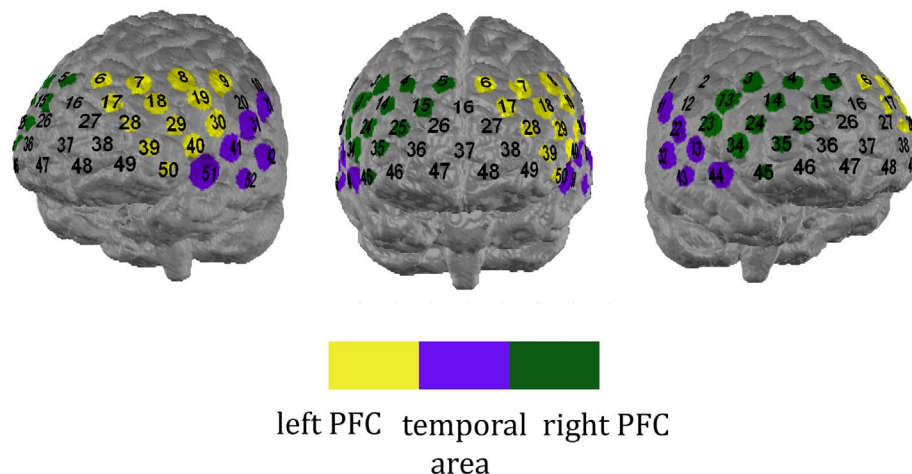Baseline sample characteristics were tested with one-way ANOVAs,

Fig. 2. Probe set arrangement with numbers indicating channels. PFC: prefrontal cortex; colour-coded channels were used for analyses. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

left PFC temporal right PFC
area

Table 2
Mean and standard deviation of reaction times (RT) and error rates (ER).

		Sham verum	Controls
RTs (ms)/ ERs			
Panic-related	Baseline	772 (122) 800 (80)	765 (116)
		3.8 (0.8) 4.0 (1.0)	4.2 (1.5)
	Post-iTBS	808 (110) 812 (90)	800 (102)
		4.1 (1.4) 4.6 (1.7)	5.4 (1.6)
Neutral	Baseline	771 (111) 799 (80)	769 (117)
		0.5 (0.8) 2.0 (1.6)	1.8 (1.4)
	Post-iTBS	802 (124) 813 (96)	790 (106)
		1.4 (1.0) 1.7 (1.5)	1.9 (1.7)

ms, milliseconds; iTBS, intermittent Theta Burst Stimulation.

$\chi 2$- or t-tests, depending on the variable in question. Fisher's exact test was used for analysing baseline sample characteristics if there were fewer than five cases per category.

To evaluate the effectiveness of patient blinding regarding the iTBS treatment condition, we conducted binomial tests of the subjectively perceived iTBS condition (test proportion: 0.5) for each group.

Regarding fNIRS data, for both ROIs, $2 \times 2 \times 3$ repeated measurement analyses of variance (RM-ANOVAs) were conducted with the within-subject factors condition (panic-related vs. neutral words) and time (pre vs. post iTBS treatment) and the between-subject factor group (verum vs. sham vs. controls). An RM-ANOVA was performed for the temporal "non-ROI".

Behavioural data (RTs and ERs) were analysed by means of RM-ANOVAs.

For the clinical data, 2×3 RM-ANOVAs were conducted with the within-subject factor time (baseline vs. post-iTBS) and the between-subject factor group (verum vs. sham vs. controls) considering differences between the three groups on the total scores (CAQ, HAM-A, PAS self-rated). The content of the subscales of all questionnaires was grouped according to the topics (as outlined in the Supplementary material) and Bonferroni-Holm-correction (Holm, 1979) was applied within each topic.

To analyse the course of iTBS effects on clinical data over time, RM-ANOVAs (7×2-design) were calculated with the within-subject factor time (from baseline to follow-up 2) and the between-subject factor group (verum vs. sham). The following post-hoc comparisons were conducted: baseline vs. post-iTBS, baseline vs. post-CBT, baseline vs. follow up 1, baseline vs. follow-up 2, follow-up 1 vs. follow-up 2, post-iTBS vs. post-CBT, post-iTBS vs. follow-up 1, and post-iTBS vs. follow-up 2 Two-tailed t-tests for matched samples were employed for post-hoc analyses.

Correlations (Spearman's rho) between the CBSI concentrations and the questionnaire subscales were calculated for the sham and verum group at baseline and post-iTBS. To do so, the difference between activation elicited by panic-related and neutral words was calculated. Changes in these CBSI concentrations (CBSI$_{post-iTBS}$ - CBSI$_{baseline}$) were correlated with changes in the questionnaire scores (post-iTBS - baseline).

Behavioural data (RTs and ERs) were available from $n = 46$ participants (20 controls, 14 verum, 12 sham patients). Due to technical problems, button presses were not recorded properly for the remaining participants and one control subject had to be excluded due a too high ER (> 2 standard deviations). Again, it was verified that groups did not differ significantly concerning baseline characteristics (Table 1).

3. Results

3.1. Sample characteristics

Table 1 shows the sample characteristics for the verum and sham

groups as well as the healthy controls. No significant group differences for sociodemographic variables were found for the complete sample or the sub-sample (values in brackets) used for the analysis of the behavioural data. For clinical ratings, no significant differences existed between verum and sham group. Compared to the control group, clinical ratings were significantly higher for both patient groups (Table 1).

3.2. Manipulation check

3.2.1. iTBS blinding check

One patient in the sham group and three patients in the verum group did not respond when asked about perceived group allocation. In the verum group, 14/19 patients guessed their treatment condition correctly, as did 16/21 in the sham group. The proportion of correct guesses differed significantly from chance (0.5) in both groups ($p = 0.027$ for sham group, $p = 0.031$ for verum group).

3.2.2. Emotional Stroop task - behavioural data

For the behavioural data, there was a significant main effect of the factor time in terms of a decrease of performance from baseline to post-iTBS regarding RTs ($F_{1,42} = 4.622$, $p = 0.037$) as well as ERs ($F_{1,42} = 5.6$, $p = 0.007$). Furthermore, a significant main effect for the factor condition ($F_{1,42} = 180, 109$, $p < 0.001$) and the factor group ($F_{2,42} = 2.42$, $p = 0.04$) was detected for ERs only. As can be seen in Table 2, all subjects committed more errors for panic-related words then for neutral words but the sham-stimulated patients generally committed the fewest errors (verum vs. sham: $t_{24} = 2.098$, $p = 0.047$; controls vs. sham: $t_{29} = 2.958$, $p = 0.006$). There were no significant interactions. Mean RTs and ERs are for all groups, times and conditions are shown in Table 2.

3.3. fNIRS data - baseline differences and treatment effects

The $2 \times 2 \times 3$ RM-ANOVAs of CBSI concentrations revealed no significant main effects, but a significant three- way interaction of condition $*$ time $*$ group for both the left ($F_{2,59} = 4.017$, $p = 0.023$) and right PFC ($F_{2,59} = 3.836$, $p = 0.027$).

For the left ROI, separate post-hoc analyses for each time point displayed a significant difference in prefrontal activation for panic vs. neutral words for the two PD patients groups at baseline whereby the patients showed less prefrontal activation in response to panic than to neutral words (sham (panic vs. neutral): $t_{20} = -2.643$, $p = 0.016$; verum (panic vs. neutral): $t_{19} = -2.126$, $p = 0.047$), but not at post-iTBS. No difference was found for the control group (Fig. 3a) at either time point.

Further post-hoc analyses of the changes of CBSI concentration over time (baseline vs. post-iTBS) in each group separately revealed a significant effect for the left PFC only in the verum group with a decrease in activation for neutral words ($t_{19} = 2.220$, $p = 0.039$) and an increase for panic-related words from baseline to post-iTBS ($t_{19} = -2.454$, $p = 0.024$) (Fig. 3b).

Comparing the three groups (verum, sham, controls) directly with each other, we further found a differentiation between the verum and the sham group for neutral words, whereby CBSI concentration was higher in the sham group ($t_{39} = 2.208$, $p = 0.033$). Concerning the right PFC, pairwise comparisons of activation for panic vs. neutral words showed no significant differences for any group at any measurement time. Similar to the results of the left PFC, there was a significant change from baseline to post-iTBS in the verum group, where the direction of change was the same as for the left PFC (increased activation for panic-related words: $t_{19} = -3.062$, $p = 0.006$, decreased activation for neutral words: $t_{19} = 2.204$, $p = 0.040$) (Fig. 3b).

Pairwise group comparisons showed significant differences in activation patterns only for post-iTBS with less activation for panic-related words ($t_{39} = -2.052$, $p = 0.047$) and more activation for neutral words ($t_{39} = 2.528$, $p = 0.016$) in the control group compared to the
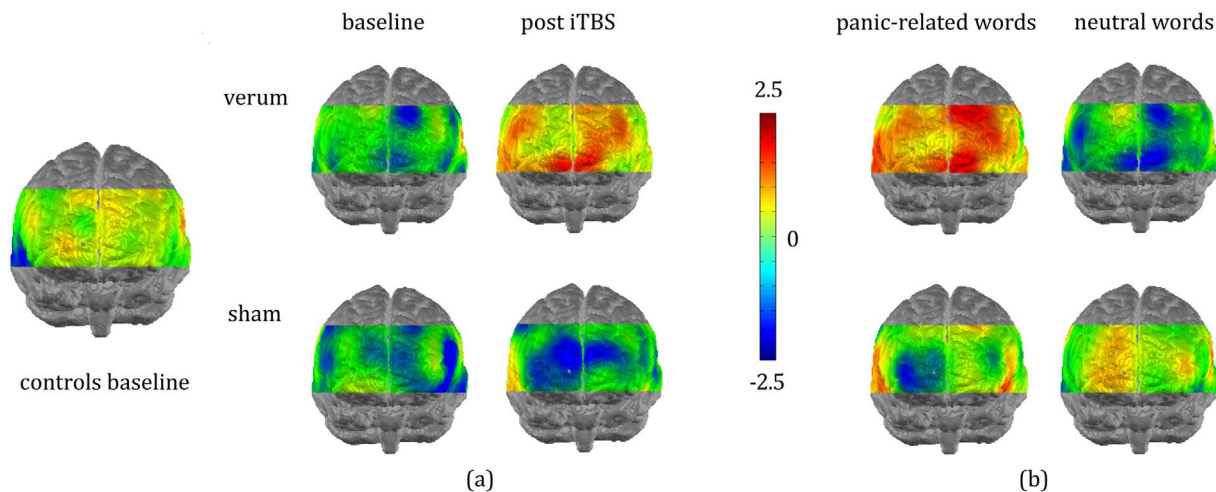
Fig. 3. a. Contrast maps panic-related words vs. neutral words for each group.
Panel a depicts differential CBSI concentration levels contrasted between the two conditions (panic-related words vs. neutral words) by means of t-values for each channel.
b. Contrast maps iTBS-related activation changes.
Panel b illustrates the changes in CBSI concentration levels from baseline to post-iTBSin the two patients groups by means of t-values for each channel, whereby positive values indicate an increase and negative a decrease in activation.

verum group. The same pattern emerged when contrasting the sham and verum group: verum-stimulated patients showed more activation for panic-related words ($t_{39} = -2.054$, $p = 0.047$) and less activation for neutral words ($t_{39} = 2.420$, $p = 0.020$). There were no significant differences in CBSI concentration levels between sham and control group for either panic-related or neutral words at any measuring time.

Regarding the RM-ANOVA for the temporal control region, no significant effects were observed.

3.4. Clinical data

For the total scores (PAS-total, HAM-A total, CAQ-total), 2×3 RM-ANOVAs revealed significant main effects for the factors time and group, as well as a significant time × group interaction (all $p \leq 0.001$). For both time points (baseline and post-iTBS), patients (verum and sham group) scored significantly higher on the clinical ratings than healthy controls. Post-hoc analyses further showed that patients' scores (verum and sham) on HAM-A-total, observer- and self-rated PAS-total and CAQ-total decreased significantly from baseline to post-iTBS. However, no significant differences between the verum and sham group were found (please refer to Deppermann et al., 2014).

For the entire group of patients (verum and sham), scores of all subscales decreased significantly from baseline to follow-up 2 after 6 months, as shown in a significant main effect of the factor time (all $p < 0.05$, for further details please refer to the supplementary material). However, there were no significant differences between the sham and verum group. Additionally, a significant interaction of time and iTBS group was found for self-rated agoraphobic avoidance (Table 3). Post-hoc analyses revealed, under sham iTBS, a significant decrease from baseline to post-CBT, follow-up 1 and follow-up 2, but a significant increase of agoraphobic symptoms from follow-up 1 to follow-up 2. Verum iTBS resulted in significantly reduced self-rated avoidance behaviour for the comparisons baseline vs. post-CBT, vs. follow-up 1 and vs. follow-up 2. Also, agoraphobic symptoms declined significantly from post-iTBS to follow-up 1 and follow-up 2 (Table 3).

For the remaining subscales, no significant interactions of time and iTBS group were found.

3.5. Correlation of fNIRS patterns and clinical data

Considering changes over time (post-iTBS - baseline), no significant correlations were discerned for the verum or sham group.

4. Discussion

In this randomised, sham-controlled iTBS study, we set out to investigate via fNIRS whether (a) we could confirm prefrontal hypoactivation in PD patients (as compared to healthy controls) during an emotional regulation task (Emotional Stroop), and if (b) this hypoactivation could be normalised over a course of 15 sessions of iTBS over the left dorsolateral PFC as an add-on treatment to state-of-the-art CBT. Additionally, we assessed the impact of iTBS on clinical symptoms and evaluated whether changes in functional activation (as assessed via fNIRS) correlated with clinical change.

As expected, a significant left lateral prefrontal hypoactivation in response to panic-related, as compared to neutral, words could be detected in both patient groups, but not in the control group prior to the beginning of treatment. The effect was restricted to the left PFC. Hence, we were able to confirm a left-lateralized reduced prefrontal response to fear-related, compared to neutral, stimuli in PD patients which did not occur in healthy controls.

Over the course of the combined iTBS and CBT intervention, this baseline prefrontal hypoactivation of the left PFC disappeared for both the sham and the verum group, pointing to a general, beneficial effect of CBT which is in line with previous studies investigating the neurobiological effects of CBT (Clark and Beck, 2010). It further speaks in favour of the assumption that one mode of action of CBT is the modification of cognitive processes which are again related to prefrontal activation (Clark and Beck, 2010). Further, when comparing changes in CBSI concentration over the course of add-on iTBS, significant alterations were only found for the verum group, whereby prefrontal activation decreased for neutral words and increased for panic-related words. These results are in line with our assumption that iTBS can enhance prefrontal activity with respect to fear-relevant stimuli. Interestingly, these treatment effects were not only found for the left hemisphere, where the stimulation occurred, but also for the right PFC. Previous studies (e.g., Ilmoniemi et al., 1997) have also reported that rTMS may cause activation changes not only in the ipsilateral, but also the contralateral hemispheres. In contrast, the sham and control group did not show significant activation changes over time.

To rule out that the iTBS-effect for the verum group merely represented a more general measurement effect without task specificity, we tested the temporal fNIRS channels for similar alterations in CBSI concentration. However, no significant activation changes were revealed for this cortical non-ROI, supporting an interpretation in terms

Table 3
Clinical course of agoraphobic avoidance behaviour from baseline to follow-up 2.

	Measurement time	Verum (n = 22) Mean (SD)	Sham (n = 22) Mean (SD)	F_{df}, p / Time, Time × group	Post hoc tests Patient group - total	Verum group	Sham group
PAS (OR) Agoraphobic avoidance	Baseline	1.91 (1.22)	1.39 (1.19)	$F_{6,252}$ = 7.91, < 0.001	Baseline > Post- iTBS *, Post-CBT***, Follow-up1***, Follow-up2***,		
	iTBS-7	1.35 (1.14)	0.96 (1.04)	ns.			
	iTBS-14	1.14 (1.23)	1.00 (1.03)		post- iTBS > Post-CBT*, Follow-up 1***, Follow-up 2**, Follow-up 2		
	post-iTBS	1.20 (1.08)	1.20 (1.24)				
	post-CBT	0.85 (1.04)	0.82 (0.99)				
	Follow- up 1	0.50 (0.77)	0.88 (0.93)		Follow-up 1 =		
	Follow-up 2	0.77 (0.92)	0.80 (1.10)				
PAS (SR) Agoraphobic avoidance	Baseline	2.03 (1.02)	1.80 (1.10)	$F_{4, 179}$ = 9.6, < 0.001		Baseline > Post-CBT*, Follow-up1***, Follow-up2**	Baseline > Post-CBT**, Follow-up1***, Follow-up2*
	iTBS-7	2.22 (1.01)	1.21 (0.91)	$F_{4,179}$ = 3.39, = 0.009			
	iTBS-14	1.97 (0.87)	1.58 (1.04)			Post- iTBS = Post CBT, Post- iTBS > Follow-up 1**, Follow-up 2*	Post- iTBS = Follow-up 1, Follow-up 2
	Post-iTBS	1.74 (0.70)	1.50 (1.14)				
	Post-CBT	1.54 (0.82)	1.11 (0.98)			Follow-up 1 = Follow-up 2	Follow-up 1 < Follow-up 2
	Follow- up 1	1.18 (0.91)	1.08 (0.86)				
	Follow-up 2	1.29 (0.89)	1.35 (0.80)				

CBT, cognitive behavioural therapy; df, degrees of freedom; F, F-value; ns., not significant; OR, observer-rated; p, p-value; PAS, Panic and Agoraphobia Scale; SD, standard deviation; SR, self-rated; Only significant ANOVA-results are depicted. P-values of ANOVA are Bonferroni-Holm corrected according to the topics described in the methods section.

* Significant at a significance level of $p \leq 0.05$.
** Significant at a significance level of $p \leq 0.01$.
*** Significant at a significance level of $p \leq 0.001$.

of iTBS-induced prefrontal activation changes to fear-related stimuli. Interestingly, this conclusion, in terms of a fear-specific modulation of prefrontal activation patterns via iTBS, is also supported by the results of our cognitive paradigm we assessed within the same study. Here we observed general prefrontal hypoactivation which was, however, not affected by iTBS application (Deppermann et al., 2014).

While we found significant clinical improvement on all questionnaires, we could not find a general therapy-enhancing effect of iTBS in the verum group. Specifically, for the verum and sham groups, we found a significant improvement of clinical symptoms from the beginning of treatment interventions to the end of iTBS treatment. Also, during the complete time course of CBT, symptom severity measured on clinical total- and subscales further improved significantly. For the total scores of the clinical ratings, differences between the sham and verum group could not be found, neither after iTBS treatment nor at the end of CBT. However, the reduction of self-rated agoraphobic avoidance was more stable over time in the verum group. Notably, agoraphobic avoidance in the verum group decreased with some temporal delay after the last iTBS session. This might be due to the general effect of CBT including the exposure session. However, delayed onset of action has also been reported for rTMS for major depression (Schutter, 2009) and might thus be a characteristic of rTMS treatment. More studies with adequate follow-up assessments are needed to clarify this matter. The lack of a general therapy-enhancing effect of iTBS add-on treatment might be a ceiling effect. Alternatively, the timing of iTBS relative to CBT might have been suboptimal. We delivered iTBS during the first three weeks of CBT, which were dedicated to psychoeducation about PD. In contrast, the active parts of CBT (i.e., exposure sessions) took place after the administration of iTBS. iTBS might have a stronger clinical effect if administered at the same time as the emotional learning, considered central to CBT (Craske et al., 2014), is actually taking place.

Looking at correlations between CBSI concentrations and clinical data, we could not find an association between treatment efficacy and changes in prefrontal activation patterns.

All participants committed more errors for panic-related than for neutral words, indicating that the Stroop paradigm did induce emotional interference as intended, in line with Dresler et al. (2012). The fact that all participants showed this effect may be due to the panic-related words (e.g. death) being associated with negative emotions not only in patients but also in the control group. In fact, an Emotional Stroop effect for negative words has been reported for healthy subjects (e.g. Bar-Haim et al., 2007). Surprisingly, sham-stimulated patients generally committed the fewest errors, whereas no differences between the verum-stimulated patients and the control group could be found. This finding is hard to interpret, but it should be kept in mind that the behavioural data were only analysed for a smaller subsample, possibly causing some effects that are not representative for the whole sample. Generally, more errors were committed at the second measurement time accompanied with an increase in RTs pointing to a motivational decrease. The missing differences in RTs between controls and PD patients might also be due to the relatively small subsample. Another explanation, given by De Cort et al. (2008), might be that external stressors like the experimental set-up (which may also increase the general stress level in the control group) can explain a missing Stroop effect.

5. Limitations

Some considerations and limitations of this study should be discussed. As in the majority of clinical rTMS studies, the insufficient blinding certainly represents a limitation. However, only patients who received verum iTBS showed an increase of panic-specific cortical activation not only in the left, but also in the right, PFC. This could indicate a more pronounced, broader cortical activation, specifically induced by verum iTBS. For future studies, sham coils evoking scalp muscle stimulations should be used (e.g., Mennemeier et al., 2010). It should further be considered that other factors, like state-dependent neural baseline activity, might also have influenced iTBS effects.

For future iTBS studies, it might be interesting to investigate its potential therapeutic add-on effects by systematically manipulating the activation of fear-relevant networks preceding iTBS application, and the timing of iTBS relative to the phase and contents of concurrent CBT. In this context, an especially interesting attempt might be the application of iTBS in order to enhance extinction learning. In fact, Guhn et al. (2014) could show that activating rTMS over the medial PFC improved the extinction of a previously conditioned fear reaction in a group of healthy adults. Regarding clinical populations, not much research exist until now. Marin et al. (2014) discusses two studies (Osuch et al., 2009; Boggio et al., 2010) were rTMS was successfully applied for improved extinction processes in groups of patients suffering from post-traumatic stress disorder. However, the authors also emphasise that further systematic studies are needed before establishing rTMS as an add-on tool in clinical applications. At last it might have been interesting to perform an additional fNIRS measurement after the completion of CBT and not just after the first weeks when additional iTBS application took place. This way it would have been possible to further analyse the duration of iTBS effects on the one hand but also the general effects of CBT on a neurobiological level in more detail.

6. Conclusion

We were able to demonstrate prefrontal hypoactivity for panic-related stimuli in PD patients, which could be normalised by add-on iTBS. Clinical ratings significantly improved during iTBS/CBT. No significant differences were found between verum and sham iTBS, except for a more stable reduction of agoraphobic avoidance in the verum group. Thus, the therapeutic potential of a combination of iTBS and CBT requires further investigation in future studies that systematically manipulate the mental activity (e.g., fear-network activation) of patients during iTBS, as well as the timing of iTBS relative to CBT contents.

Conflict of interest

The authors declare that they have no conflict of interest.

Contributors

VA, A-CE, AJF and PZ designed the study and wrote the study protocol. SD, NV, SS, FBH, SN, TD and IL recruited participants and analysed data. SD conducted fNIRS measurements. NV, SD and SS

conducted CBT. SD, NV, and JD wrote the manuscript. All authors have contributed to and approved of the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2017.09.013.

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