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

Saskia Deppermann, Nadja Vennewald, Julia Diemer, Stephanie Sicking, Florian B. Haeussinger, Thomas Dresler, Swantje Notzon, Inga Laeger, Volker Arolt, Ann-Christine Ehli, Andreas J. Fallgatter, Peter Zwanzger

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

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

Saskia Deppermann, Nadja Vennewald, Julia Diemer, Stephanie Sicking, Florian B. Haeussinger, Thomas Dresler, Swantje Notzon, Inga Laeger, Volker Arolt, Ann-Christine Ehli, Andreas J. Fallgatter, Peter Zwanzger

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: 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

Abbreviations: ANOVA, analysis of variance; CAQ, Cardiac Anxiety Questionnaire; CBSI, correlation-based signal improvement; CBT, cognitive-behavioural therapy; ER, error rate; fNIRS, functional near-infrared spectroscopy; HAM-A, Hamilton Anxiety Rating Scale; HHb, deoxyhemoglobin; iTBS, intermittent Theta Burst Stimulation; LOCF, last observation carried forward; O2Hb, oxyhemoglobin; PD, panic disorder; PAS, Panic and Agoraphobia Scale; PFC, prefrontal cortex; RM-ANOVA, repeated-measures analysis of variance; ROI, region of interest; RT, reaction time; rTMS, repetitive Transcranial Magnetic Stimulation

* Corresponding author.

E-mail address: Saskia.Deppermann@med.uni-tuebingen.de (S. Deppermann).

Both authors contributed equally to this work and are therefore both considered as first authors.
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 hypo-activation 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 neuro-biological 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-situational 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 ×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
دریافت فوری متن کامل مقاله

امکان دانلود نسخه تمام متن مقالات انگلیسی
امکان دانلود نسخه ترجمه شده مقالات
پذیرش سفارش ترجمه تخصصی
امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
امکان دانلود رایگان ۲ صفحه اول هر مقاله
امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
دانلود فوری مقاله پس از پرداخت آنلاین
پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات