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Preliminary communication

Treatment of major depression with bilateral theta burst stimulation: A randomized controlled pilot trial

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ABSTRACT

Background: Current efforts to improve clinical effectiveness and utility of repetitive transcranial magnetic stimulation (rTMS) in the treatment of major depression (MD) include theta burst stimulation (TBS), a patterned form of rTMS. Here, we investigated the efficacy of bilateral TBS to the dorsolateral prefrontal cortex (dlPFC) in patients with MD in additon to ongoing medication and psychotherapy.
Methods: In this randomized-controlled trial, thirty-two patients with MD were treated for six weeks (thirty sessions) with either successively intermittent, activity enhancing TBS (iTBS) to the left and continuous, inhibiting TBS (cTBS) to the right dlPFC or with bilateral sham stimulation. Primary outcome measure was the proportion of treatment response defined as a Montgomery–Åsberg Depression Rating Scale (MADRS) $\leq 50\%$ compared to baseline. Secondary outcomes comprised response and remission rates of the Hamilton Depression Rating Scale (HAMD) and the Beck Depression Inventory (BDI).
Results: A larger number of responders were found in the cTBS ($n=9$) compared to the sham-stimulation ($n=4$) group (odds ratio: 3.86; Wald $\chi^2=3.9$, $p=0.048$). On secondary endpoint analysis, patient-reported outcome as assessed by the BDI, pointed towards a higher rate of remitters in the cTBS ($n=6$) than in the sham ($n=1$) group (odds ratio: 9; Wald $\chi^2=3.5$, $p=0.061$).
Limitations: With regard to the pilot character of the study and the small sample size, the results have to be considered as preliminary.
Conclusions: These findings provide first evidence that six weeks treatment of MDD with iTBS to the left and cTBS to the right dlPFC for six weeks is safe, feasible and superior to sham stimulation applied add-on to pharmacological and psychotherapeutic treatment.

1. Introduction

High-frequency repetitive transcranial magnetic stimulation (rTMS) applied to the left dorsolateral prefrontal cortex (dlPFC) has been established as an effective treatment for major depressive disorder (Slotema et al., 2010; Fitzgerald and Daskalakis, 2012; Lee et al., 2012; George et al., 2013). It is currently recommended for moderately depressed patients when an initial treatment with antidepressant medication and psychotherapy failed (George and Post 2011). Nevertheless, considerable efforts are currently made to further enhance effectiveness and utility of rTMS as a treatment in major depression (Kammer and Spitzer, 2012).

Up to now, effects in larger controlled studies were predominantly shown in subjects treated with rTMS as monotherapy (O'Reardon et al., 2007; George et al., 2010; Herwig et al., 2007). Therefore, it is conceivable that improvements of effectiveness by optimizing stimulation protocols would considerably increase the number of patients eligible for rTMS treatment. In addition, the mode of action different from pharmacological and psychotherapeutic approaches points towards additive or even synergistic effects that most likely have not yet reached their full potential.

Recently, theta burst stimulation (TBS), a patterned form of rTMS with brief stimulation sessions has been put forward as a new option to induce a more effective modulation of cortical activity (Huang et al., 2005). The investigation of therapeutic effectiveness of this alternative stimulation paradigm for the treatment of various neuropsychiatric disorders has produced variable results (Eberle et al., 2010; Benninger et al., 2011; Plewnia et al., 2012). However, open studies have provided first preliminary evidence for an antidepressant effect of TBS (Chistyakov et al., 2010; Holzer and Padberg, 2010).

As regards the efforts to improve effectiveness of rTMS treatment, sequential bilateral stimulation and extended number of pulses per session have been put forward as potential methods to

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optimize existing unilateral stimulation protocols (Fitzgerald et al. 2006; Berlim et al. 2012) although recent studies have not found superior efficacy (Fitzgerald et al. 2012). Nevertheless, available data suggest that rTMS treatment courses up to 6 weeks or more may be suitable to enhance the effectiveness of rTMS treatment of MD (O'Reardon et al. 2007; George and Post, 2011).

In order to proceed on the development of effective rTMS treatment protocols of depression, we conducted a randomized, sham-controlled trial applying 6 weeks of sequential facilitatory intermittent TBS (iTBS) to the left and inhibitory continuous TBS (cTBS) to the right dlPFC as an add-on treatment. We hypothesized that this innovative protocol would yield a greater therapeutic effect than sham stimulation in patients on regular treatment with antidepressants and psychotherapy.

2. Methods and materials

2.1. Subjects

Patients were recruited from the in-patient units of the department of Psychiatry and Psychotherapy at the University Hospital of Tübingen. Inclusion criteria were right-handedness, age 18–75 years, with a DSM-IV diagnosis of MD, single episode or recurrent. Exclusion criteria for study participation included inability to give informed consent, seizures in medical history, neurological disorders, previous brain injuries, ferromagnetic implants in the brain, deep brain stimulation, cardiac pacemaker, psychotic symptoms, substance abuse, pregnancy, Benzodiazepines other than Lorazepam > 1 mg/d.

All patients of the study were on antidepressant medication at least for 2 weeks before randomization and remained so until the end of the trial. Antidepressant medications of the participating patients were: Mirtazapine ($n=4$, 7.5–45 mg/d), Venlafaxine ($n=2$, 75–150 mg), Amitriptyline ($n=1$, 50 mg), Paroxetine ($n=2$, 10–20 mg), Sertraline ($n=1$, 50 mg), Trimipramine ($n=1$, 50 mg), Citalopram ($n=1$, 40 mg), Escitalopram ($n=1$, 5 mg), Bupropion ($n=1$, 300 mg), Quetiapine ($n=1$, 250 mg), Lithium ($n=1$, 675 mg). In 10 patients (cTBS: $n=6$; Sham: $n=4$) the antidepressant medication was changed during the course of TBS treatment. Treatment resistance was defined as no response to two different antidepressant medications and one combination of treatment with treatment periods of at least 4 weeks each in sufficient dosage for the current episode (Herwig et al. 2007).

2.2. Study overview

In this randomized, sham-controlled trial, thirty-two patients were randomly assigned (16:16) to receive iTBS over the left dlPFC and cTBS over the right dlPFC or a sham stimulation over both hemispheres. Patients were randomized using a single computer-generated random number sequence. The patients and raters were blind to the treatment condition.

Participants gave informed consent for a protocol following the Declaration of Helsinki, and the study was approved by the Institutional Review Board of the University of Tübingen Medical Faculty. The study was registered at ClinicalTrials.gov (Identifier: NCT01153139).

2.3. rTMS procedures

TMS was applied using a Magstim Super Rapid (The Magstim Company Ltd, Whitland, UK) with a figure-eight coil (diameter of each winding: 70 mm, biphasic stimuli of 250 μs). The individual resting motor threshold (MT) was determined bilaterally at the beginning of the first treatment session and defined as the minimal intensity needed to obtain a muscle twitch of the contralateral thumb in at least 5 of 10 stimuli. Stimulation (cTBS and iTBS) intensity was standardized at 80% of MT and applied successively to each hemisphere in alternating order. The dlPFC treatment sites were located by 10–20 EEG electrode placement system with F3 and F4 indicating the left and right stimulation areas (Herwig et al., 2003). Each stimulation session consisted of two trains of 600 stimuli applied in bursts of 3 pulses at 50 Hz given every 200 ms. Left-sided stimulation with iTBS was applied 20 times for 2 s every 10 s. Right-sided stimulation with cTBS was applied continuously for 40 s. Patients received rTMS treatment each working day for 6 weeks (30 sessions). The coil was hand-held during stimulation trains to allow for optimal fixation. All patients were seated in a comfortable chair while they were receiving stimulation treatment.

For adequate masking of the patients, sham stimulation was performed with the coil angled at 45° and 5 cm lateral to F3 and F4 above the temporal muscle (Herwig et al., 2007). Thus, sham stimulation is accompanied by similar auditory (clicking noise) and somatosensory (pricking, twitches of the temporal muscle) artifact. The patient and raters remained blind to the type of treatment until completion of the final data analysis.

2.4. Efficacy assessment

The primary effective outcome measure was response to treatment defined as Montgomery–Åsberg Depression Rating Scale (MADRS) reduction of 50% or more compared to baseline at the end of the treatment. Secondary outcome measures comprised treatment response as assessed with the Hamilton Depression Rating Scale (HAMD ≤ 50% baseline) and the Beck Depression Inventory (BDI ≤ 50% baseline as well as the equally dichotomous variable of depression remission defined as MADRS and HAMD ≤ 7 and BDI ≤ 8 (Frank et al., 1991). MADRS and BDI were obtained by the attending psychiatrist at baseline and after every week during the course of treatment. HAMD was measured before and after the end of treatment. Safety was monitored at every treatment visit by spontaneous adverse event reports.

2.5. Statistical analysis

Statistical calculations were performed with SPSS 20.0 (SPSS Inc., www.spss.com). In order to assess whether bilateral TBS compared with sham stimulation increased treatment response (predefined primary outcome measure) and remission rate, a logistic regression model according to a previous major TMS treatment trial (George et al., 2010) was applied with the independent variables of *treatment condition* (TBS vs. sham), *treatment resistance* (yes vs. no), *current depressive episode duration* (months), and *age* (years). The current depressive episode duration was log transformed to reduce the variance and the detrimental effect of outliers. The sample size of 32 was chosen in order to have 80% probability to recognize a significant (at a two-tailed alpha level of 0.05) large increase of response rate, specifically from an expected 0.2 in the sham group (1 of 5 subjects) up to 0.67 in the TBS group (2 of 3 subjects). Unless stated otherwise, data were analyzed by intention to treat (ITT) defined as all randomized patients who received at least one treatment session. Missing values were imputed by carrying the last observation forward. The alpha level was set at 0.05 for all tests.

3. Results

Baseline characteristics of the participants are summarized in Table 1. There were no significant differences between the groups.