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Different forms of prefrontal theta burst stimulation for executive function of medication- resistant depression: Evidence from a randomized sham-controlled study

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ABSTRACT

Background: Even during symptomatic remission, many patients with medication resistant depression (MRD) still demonstrate impaired cognitive function, especially executive function (EF). Theta-burst transcranial magnetic stimulation (TBS) modulates cortical excitability and may treat MRD. Evidences from previous studies show that intermittent TBS (iTBS) produces cortical excitatory effects, while continuous TBS (cTBS) produces a reduction of cortical excitability. EF is highly dependent on prefrontal activity, but the effects of different forms of prefrontal TBS on EF remain unknown.
Methods: 60 MRD patients were recruited and randomly assigned to one of four groups. Treatment was determined by the group to which an individual was assigned; A: cTBS 1800 pulses/session; B: iTBS 1800 pulses/session; C: a combination of cTBS + iTBS, 1800 pulses/session for each; and D: sham TBS. Wisconsin Card Sorting Test (WCST) for the performance of EF was evaluated before and after 10 daily treatment sessions
Results: Repeated measures ANOVA, with each WCST index at baseline and 2 weeks after TBS as within-subject factors, demonstrated that a statistically significant interaction of TBS groups (G) and antidepressant responses [(R), responses were defined as >50% reduction of depression scores after 2-weeks TBS treatment] on the before-versus-after changes of all WCST indexes ($G \times R$, $p < 0.05$). Responders in Group B, but not in the other groups, showed a significant improvement in WCST performance. Only nonresponders in Group A showed a trend for EF worsening.
Conclusions: Our findings showed that left prefrontal iTBS, not right prefrontal cTBS, improved EF, and this can be independent from its antidepressant effects.

1. Introduction

Major depressive disorder (MDD) is a mental disorder characterized by persistent low mood, and loss of interest or pleasure in normally enjoyable activities. Besides mood disturbance, MDD is also associated with impairments in multiple domains of cognitive function, including language, attention, and executive function (EF) (Ottowitz et al., 2002). During symptomatic remission, some MDD patients still demonstrate impaired cognitive function, especially EF, which is associated with prefrontal dysfunction (Eiji Ikeda et al., 2013; Alvarez & E.E., 2006; Li et al., 2010a; Nowrangi et al., 2014). Cognitive dysfunction is a main cause for dissatisfaction with functional performance and is associated with worsened long-term outcome in MDD patients (Aretouli & B.J., 2010). So far no antidepressant medications effectively treat such cognitive problems (Kameyama et al., 2006).

Repetitive transcranial magnetic stimulation (rTMS) at prefrontal cortex is a treatment option for treatment-refractory depression. There is evidence that rTMS brings not only mood improvement, but is also associated with amelioration of neurocognitive dysfunction in adult patients (Padberg et al., 1999; Martis et al., 2003; Fitzgerald et al., 2003; Holtzheimer et al., 2004; Luber & L.S., 2014). In one of the different protocols of rTMS, prefrontal rTMS seems to result in an increase of prefrontal function, a normalization of cortico-limbic dysregulation (Li et al., 2010b), and a restoration of prefronto-thalamic functional connections (Li et al., 2013). Hence, according to the previous literatures, prefrontal rTMS may have a benefit effect on EF and according to that EF is highly dependent on prefrontal activity (Alvarez & E.E., 2006; Li et al., 2010a; Nowrangi et al., 2014)..

Theta-burst stimulation (TBS), a variant form of rTMS, is a safe and well-tolerated treatment option for MDD (Li et al., 2014). Previous TBS

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studies on motor cortex demonstrated that the TBS induction of after-effects on synaptic plasticity is more rapid than traditional rTMS protocols and has less irritating side effects. TBS can also produce a consistently sustained change in synaptic plasticity by acting with N-methyl-D-aspartate receptor, which effect may be longer than the duration of the TMS intervention (Huang et al., 2005) (Huang et al., 2007). TBS is a promising tool in treating depressive symptoms (Li et al., 2014). However, the effects of prefrontal TBS on cognitive function in MDD patients remain unclear.

The present study compared the effects of different forms of prefrontal TBS on EF, as assessed using the Wisconsin Card Sorting Test (WCST), in medication-resistant depression (MRD). According to the previous TBS studies, enhancing prefrontal excitability by left sided repetitive rTMS was positively associated with improvement of EF (Martis et al., 2003). We hypothesized the TBS protocols involving iTBS, typically associated with excitatory effects, delivered over left prefrontal cortex would have better effects on EF in comparison to cTBS, usually associated with inhibition of cortical excitability.

2. Materials and methods

2.1. Subjects

Subjects were 60 adult patients of 21–70 years of age, with a DSM-IV diagnosis of recurrent major depressive disorder, which was diagnosed after a thorough medical history check and performing a semi-structured interview by administering the Mini International Neuropsychiatric Interview (MINI). The recruited patients were those who failed to respond to at least two antidepressant treatments given with typically adequate dosages and durations. Additionally, the current depressive episode had to have a Clinical Global Impression Scale (CGI-S) score of at least 4 and a total score of at least 18 on the Hamilton Depression Rating Scale-17 (HDRS-17) (Hamilton, 1967), allowing recruitment of patients with moderate to severe depression.

Exclusion criteria were if patient had a history of psychotic disorders, bipolar I or II disorders; substance abuse or dependence; personality disorder (based on DSM-IV criteria); a lifetime medical history of major systemic illness or neurological disorders (e.g. seizure, stroke, post-brain surgery, traumatic brain injury); brain implants (neurostimulators) or cardiac pacemakers; or if they were pregnant.

2.2. Study overview

The study included two parts. First, the patients went through one week of health screening and tests, including brain structural imaging by MRI and routine laboratory tests, such as complete blood count, biochemistry and thyroid tests, to ensure that the patient was medically stable. This was followed by two weeks of treatment, which included daily treatment with active TBS or sham stimulation (throughout the study, patients were required to remain on their original medication regimen). Patients were randomized 1:1:1:1 into 4 TBS groups (Groups A, B, C and D, see below for stimulation parameters). During treatment, one TBS session was scheduled daily for 5 consecutive days, with a total of 10 sessions delivered over the 2 week treatment period. The study was performed in accordance with the Declaration of Helsinki and was approved by the local Ethics Review Committee. All participants provided written informed consents after the nature of the procedures had been clearly explained.

2.3. Theta-burst stimulation parameters and session procedures

The TBS sessions were delivered using a Magstim Rapid2 stimulator (Magstim Company, Ltd). The target site of stimulation, the dorsolateral prefrontal cortex, was defined as a point between the junction of Brodmann area (BA) 9 and 46 by referral to each patient's brain MRI scan and we used brain-navigation computer software and an infrared system (Brainsight, Rogue Research, Inc., Montreal, QC) to guide the coil to target the point over the patient's head (CT et al., 2010). The TBS parameters we adopted followed the standard TBS protocols, with 3-pulse 50-Hz bursts given every 200 ms (at 5 Hz) and an intensity of 80% active motor threshold (AMT), as measured by using a handheld 700-mm figure-of-eight coil (Huang et al., 2005). Every day before TBS, we determined AMT for the contralateral abductor pollicius brevis muscle (APB) by using a visualization of movement method (Pridmore et al., 1998). The stimulation intensity for AMT was defined for the Magstim stimulator as the minimum single pulse intensity required to induce a contraction of the APB on more than five out of ten trials, while the subject was maintaining a voluntary contraction of about 20% of maximum.

In continuous TBS, a 120-s train of uninterrupted bursts was given to the right dorsolateral prefrontal cortex (1800 pulses) in each session per day. In intermittent TBS, a 2-s train of bursts was repeated every 10 s for a total of 570 s (1800 pulses) to the left dorsolateral prefrontal cortex in each session per day. Patients in Group A received continuous TBS (1800 pulses/session, total 10 sessions); Group B received intermittent TBS (1800 pulses/session, total 10 sessions); Group C received a combination of intermittent and continuous TBS (intermittent TBS-1800 + continuous TBS-1800 pulses/session, total 10 sessions; randomly assigned which TBS started first); and Group D received sham TBS (bursts given as continuous TBS or intermittent TBS, randomly assigned; 1800 pulses/session, total 10 sessions) with the coil set at 90-degree to the skull.

2.4. Neurocognition and depression assessments

EF and depression were assessed at baseline (Week 0, before TBS treatment) and at the end of the 2-week TBS treatment (1 h after the last session of the TBS stimulation, Week 2). WCST, used in neuropsychological test extensively and designed to measure frontal lobe impairment, has a long history to be a probe of executive functioning. We evaluated the primary efficacy outcome by using indices of WCST by computer for the performance of EF that included total correct, total errors, percentage errors (% errors), percentage conceptual level responses (% CLR), and categories completed (CC). Severity of depression was measured by HDRS-17. For mood improvement, responders were defined as those who had at least 50% reduction in their baseline HDRS-17 at the end of Week 2.

2.5. Statistical methods

Statistical analysis of demographic and clinical data was performed using SPSS16.0 (SPSS Inc). A one-way ANOVA (or Student's t-test) and Fisher's chi-square test (or Yate's correction) were used to compare the continuous and categorical variables among groups, respectively. p-Values of less than 0.05 were deemed statistically significant.

Pearson's correlation analysis was applied to investigate relationships between clinical ratings (i.e. HDRS-17, CGI-S). Antidepressant effects of time and group were determined by Student's t-test and ANOVA. The least significant difference (LSD) was used for post-hoc analyses.

Repeated measure ANOVA (rmANOVA) was carried out with three independent factors: time (Week 0 and Week 2) as a within-subject factor, TBS groups (G) and antidepressant response (R) as between-subject factors. Dependent variables were changes in WCST indices between Week 0 and Week 2, including total correct responses, total errors, error rate, conceptual level response rate and completed categories. As there were small sample sizes in subgroups (e.g., responders, non-responders), Wilcoxon signed-rank tests were performed to compare the before-versus-after changes of all WCST indices in a subgroup analysis. ANCOVA was performed to evaluate (1) the difference of indices of EF at baseline in each group, adjusted by sex and age (2) the effect of HAMD score's change [(Week 2 − Week 0)/Week 0] on the change of indices of WCST.