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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.

3. Results

All patients, except one in Group A, completed the evaluations for EF and depression at both Week 0 and Week 2. The one failure to complete the post-TBS assessment was due to negative impact from persistent depression after 2 weeks of TBS treatment. Baseline demographics and clinical features (age, gender, CGI-S scores and HDRS-17 scores) showed no significant difference among four groups.

These subjects all took part in a previous study. The effects of the TBS delivered on depression have previously been reported in greater detail (Li et al., 2014). In short, regarding the changes of HDRS-17 scores between Week 0 and Week 2, active groups (Group A: −22.5%; Group B: −42.3%; Group C: −52.5%) showed large improvements in HDRS-17 scores; however, the sham group (Group D: −17.4%) didn't improve as much as the active groups did. The ACOVA analysis demonstrated that there was a significant difference between the four groups (F-value = 6.166; $p = 0.001$). The post-hoc analysis revealed that there were significantly greater improvements of HDRS-17 scores in Group B and Group C than in Group A and Group D, while there was no significant difference between Group A and Group D (Li et al., 2014)..

Table 1 demonstrates the analytical results based on group (G: A, B, C, D) and antidepressant response (R: response or non-response). As for EF, rmANOVA showed a significant interaction between G and R on measures of the WCST (GxR, $p = 0.008$ for total correct responses; $p = 0.046$ for total errors; $p = 0.041$ for error rate; $p = 0.046$ for conceptual level response rate; $p = 0.018$ for completed categories).

Wilcoxon signed-rank tests show that significant differences between baseline and post-TBS in WCST indices were found only for Responders in Group B ($p = 0.027$ for total correct responses; $p = 0.027$ for total errors; $p = 0.028$ for errors rate; $p = 0.028$ for conceptual level response rate; $p = 0.028$ for completed categories) (Table 1) (Fig. 1). No significant before-versus-after changes were found in the other groups. However, there was a trend for differences in some indices within subgroups, including an improved conceptual level response rate of Non-Responders in Group B ($p = 0.097$) and a worsening of competed categories of Non-Responders in Group A ($p = 0.059$) (Table 1).

In Group B, responders improved significantly after 2-weeks of TBS on the index of total correct responses than non-responders ($p = 0.036$) (Fig. 2). There were no significant between-group differences on the other WCST indices (Fig. 2).

ANCOVA showed that (1) there was no statistically significant between responder and non-responder in the WCST indices at baseline (total errors, % errors, % CLR, CC) except total correct (in the supplement table) and (2) there was no significant effect of HAMD score's change on the change of indices of WCST ($p = 0.872$ for total correct responses; $p = 0.146$ for total errors; $p = 0.872$ for error rate; $p = 0.107$ for conceptual level response rate; $p = 0.186$ for completed categories).

4. Discussion

To our knowledge, this is the first double-blind sham-controlled study reporting cognitive effects of TBS when it is employed as an effective antidepressant treatment (Li et al., 2014). Our findings suggested that the best parameter for TBS in the treatment of depression (at least of those tested in the current study), in terms of both antidepressant and cognitive-enhancing effects, was left prefrontal iTBS alone. The supporting evidence was that a combination of left prefrontal iTBS and right prefrontal cTBS did not show significantly better antidepressant efficacy than left prefrontal iTBS alone. In addition, only the responders of the left prefrontal iTBS group (Group B) had significant improvement on EF. Since the cognitive effect did not occur in the responders of the other three groups, the observed cognition-enhancing effect was independent from the antidepressant effect, which was also compatible with our further analyses between change of HAMD score and change of indices of WCST. Moreover, non-responders who received iTBS, but not a combination of cTBS + iTBS, also had a trend for

Table 1
TBS effects on executive function.

WCST indices	A: cTBS		B: iTBS		C: cTBS + iTBS		D: Sham		p-Value[a] G, R, G × R
	Non-responders (n = 11)	Responders (n = 3)	Non-responders (n = 9)	Responders (n = 6)	Non-responders (n = 5)	Responders (n = 10)	Non-responders (n = 13)	Responders (n = 2)	
Total corrects									
Baseline	64.6(17.3)	73.7(15.1)	72.9(15.3)	41.7(16.0)	64.8(16.8)	68.4(22.5)	55.6(18.5)	96.5(6.4)	G(0.227)
Post-TBS	68.5(19.8)	76.0(12.5)	67.3(18.5)	60.8(12.3)	68.2(10.0)	67.4(18.9)	60.2(19.2)	91.0(15.6)	R(0.207)
p for time[b]	0.441	0.593	0.110	***0.027****	0.588	0.721	0346	0.655	G × R(***0.008****)
Total errors									
Baseline	53.3(27.0)	25.3(11.5)	39.0(24.5)	78.0(33.5)	43.4(32.8)	46.3(31.4)	66.1(28.9)	30.5(7.8)	G(0.710)
Post-TBS	48.6(29.0)	21.0(15.6)	32.0(32.4)	50.7(30.4)	34.6(24.5)	43.6(32.0)	60.1(29.4)	32.0(22.6)	R(0.482)
p for time[b]	0.284	0.414	0.173	***0.027****	0.104	0.759	0.184	0.655	G × R(***0.046****)
% Errors									
Baseline	43.4(18.9)	24.7(6.7)	33.0(17.1)	62.2(23.5)	36.8(23.3)	37.8(22.8)	52.2(21.3)	24.0(5.7)	G(0.714)
Post-TBS	39.2(21.2)	20.0(8.7)	28.3(23.5)	41.3(22.6)	30.8(16.2)	35.8(23.1)	47.5(21.9)	26.0(17.0)	R(0.437)
p for time[b]	0.284	0.285	0.137	***0.028****	0.138	0.683	0.113	0.655	G × R(***0.041****)
% Conceptual level responses									
Baseline	43.9(26.6)	71.0(8.9)	57.2(23.0)	22.0(29.4)	54.6(33.1)	52.2(30.7)	34.5(27.9)	70.5(10.6)	G(0.735)
Post-TBS	48.2(28.2)	76.3(11.6)	65.1(30.1)	45.2(32.8)	61.0(23.6)	52.2(33.5)	38.2(29.9)	66.0(26.9)	R(0.447)
p for time[b]	0.168	0.285	0.097	***0.028****	0.225	0.959	0.401	0.655	G × R(***0.046****)
Completed categories									
Baseline	2.8(2.4)	5.7(0.6)	4.3(2.2)	1.7(2.4)	4.4(2.6)	4.1(2.2)	2.2(2.2)	5.0(1.4)	G(0.794)
Post-TBS	2.4(2.5)	5.3(1.6)	4.8(2.4)	2.8(2.9)	4.4(2.2)	3.5(2.4)	2.1(2.0)	4.5(4.1)	R(0.340)
p for time[b]	0.059	0.317	0.414	0.180	1.000	0.167	0.862	0.655	G × R(***0.018****)

Note. WCST: Wisconsin Card Sorting Test; iTBS: intermittent theta-burst stimulation; cTBS: continuous theta-burst stimulation.

[a] Repeated-measure ANOVA: time (i.e.: WCST sub-scores at baseline and 2 weeks after TBS) as within-subject factors; TBS group (**G**, i.e.: Groups A, B, C, D) and antidepressant response (**R** i.e.: responders and non-responders) as between-subject factors; main effects of G and R as well as interaction of G and R (**G** × **R**) were reported with a p-value of less than 0.05 as statistically significant. Responders were defined as those with an above 50% reduction in depression scores after 2-weeks of TBS treatment.

[b] Non-parametric analysis (NPr) with Wilcoxon signed rank test was used for paired (baseline vs. post-TBS) and small sample sizes when divided into responders and non-responders.

* $p < 0.05$.

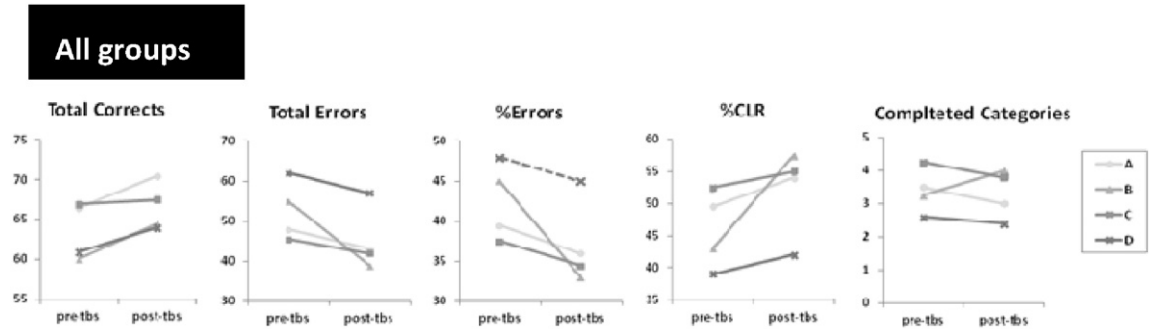

Fig. 1. The changes in indices of the Wisconsin Card Sorting Test after prefrontal intermittent and/or continuous theta-burst stimulation (iTBS and/or cTBS). The before-versus-after changes of total correct responses, total errors, % errors and % conceptual level responses (%CLR) among the four groups showed a similar trend. Group B (shaped in triangle), but not group C, had significantly more improvement than other groups in many of the indexes including total errors, % errors, %CLR, and completed categories. Group A: cTBS; Group B: iTBS; Group C: cTBS + iTBS; Group D: sham.

enhanced EF. A trend toward worsening EF in non-responders of Group A (i.e., cTBS on the right DLPFC) was observed.

As hypothesized, the best cognitive improvement in the left prefrontal excitatory iTBS group was not unexpected. iTBS typically induces a long-term potentiation-like effect, which here may have elevated left prefrontal cortex function and resulted in better EF; while cTBS typically induces long-term depression of cortical excitability, which might to some extent suppress any potentiation effect of iTBS in Group C. These results were consistent with previous literature that enhancing prefrontal excitability by left-sided repetitive transcranial magnetic stimulation was positively associated with improvement of EF (Martis et al., 2003; Moser et al., 2002). Moser et al. recruited 19 elderly, drug resistant depressed subjects to undergo left prefrontal active (n = 9) or sham (n = 10) rTMS (80% motor threshold (MT), 20 Hz, 5 sessions in a week) to assess antidepressant and cognitive effects. Although both groups showed a significant reduction in HDRS scores, an enhanced Trail Marking Test-B score was only reported in the active rTMS group. This finding supported that excitatory TMS effects on the left DLPFC could result in mood-independent improvement in EF (Moser et al., 2002). In another open study with severely depressed patients, Martis et al. demonstrated that a left prefrontal high frequency rTMS group had a significant improvement in working memory-executive function regardless of changes in mood (110%, 10 Hz, 10 sessions/2 weeks or 20 sessions/4 weeks) (Martis et al., 2003).

In contrast, some studies have not found a statistically significant enhancement of EF following left-sided high frequency rTMS, compared with either sham stimulation or other stimulation groups (Boggio et al., 2005; Jorge et al., 2004; Mogg et al., 2008). For example, Boggio et al. performed high frequency rTMS (110% MT, 15 Hz, 10 daily sessions) over the left DLPFC to treat 25 patients with depression and Parkinson's disease. The authors assessed cognitive effects with real 15 Hz rTMS with a placebo drug group and sham TMS with a fluoxetine group. Both groups showed improvements in EF and visuospatial ability, but there was no significant difference between the two groups. For such non-significant results, small sample sizes and the lack of a sham group without active antidepressants might be one reason why treatment groups showed no statistically significant difference (Boggio et al., 2005). Additionally, differences in targeting strategies for neurostimulation also might play a role in the neurocognitive effects of stimulation. Sack et al. had performed a study and illustrated groups targeting by 10/20 EEG system needed more fivefold effect size than by structural MRIs or group-analyzed fMRI navigation to reveal statistically significant behavior impact of right parietal TMS using different positioning approaches (Sack et al., 2009). In addition, different from the previous articles, we demonstrated neurocognitive effects by using TBS, which had been shown to produce more sustained effects on cortical activity, compared to rTMS (Huang et al., 2005). In our study, using structural MRI neuronavigation, a double-blind sham control design and stimulation by TBS, we increased the chances of seeing significant effects on EF. Moreover, our results not only confirmed that dorsolateral prefrontal cortex was highly associated with executive function (Alvarez & E.E., 2006; Nowrangi et al., 2014), but also indicated that left-sided dorsolateral prefrontal cortex may be more important for EF, at least in the depressed group investigated.

The finding of no improvement in neurocognitive effects with right-sided continuous TBS stimulation (Group A) is not surprising although the cortical excitability of right DLPFC was presumably suppressed. In previous literature, there are several studies in line with our study results (Group A) (Januel et al., 2006; Fitzgerald et al., 2009). Januel et al. performed a double-blind sham-controlled study using right prefrontal rTMS (90% of the MT, 1 Hz, total 16 session/4 weeks) to test for antidepressant effects and neurocognitive effects. No significant differences in the Trail Making Test (TMT) A/B and Stroop tests were found between active and sham groups (Januel et al., 2006). However, one recent study showed that inhibition of the right DLPFC by TBS resulted in a decrease in anticipatory fixations in a number search task (Luthi et al., 2014). Further investigations of inhibitory stimulation over right DLPFC and changes of cognitive functions are needed for clarification. In our study, we found a worsening index of completed categories on the WCST in non-responders of Group A. Additionally, compared to the responders, a positive finding of neurocognitive enhancement in Group B was observed, but a similar effect was not seen in Group C, which yielded the best antidepressant efficacy. It may be that an opposite cognitive effect for right DLPFC cTBS and left DLPFC iTBS

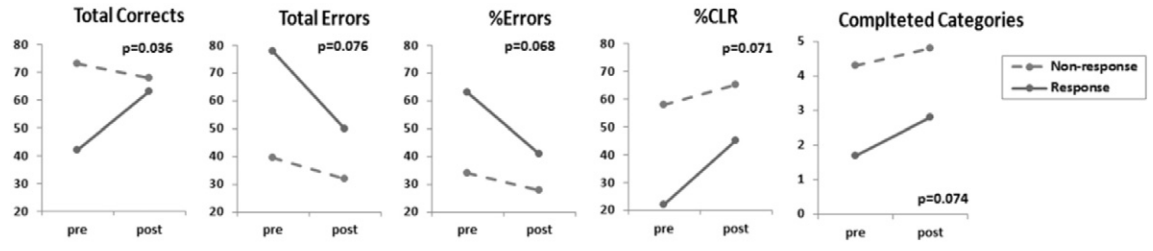

Fig. 2. The changes of responders and non-responders in Group B. Responders had significantly greater improvement in total correct response than non-responders ($p = 0.036$).

might contribute to the result. Right cTBS seemed to partially suppress the potentiation effect on EF from left iTBS. In another PET study, we also found that a separate cohort of MRD patients had decreased regional cerebral glucose metabolism in bilateral prefrontal cortex compared with non-MRD and control groups (Li et al., 2015). Right-sided prefrontal cTBS, which was associated with inhibition of cortical excitability, could have the potential of worsening prefrontal function in the MRD patients. We concluded the best parameter of TBS in the treatment of depression from those investigated, in terms of both antidepressant and cognitive-enhancing effects, was left prefrontal iTBS alone.

With regard to the TBS mechanisms in depressive patients, however, associated literature remains in its infancy, so we have tried to explain the potential neuro-network modulation in our study by referral to past rTMS investigations. In previous studies, high-frequency prefrontal rTMS treatment seemed to result in a cascade of neurobiological changes in remote limbic regions linked with the stimulated prefrontal cortex, such as the anterior cingulate cortex, striatum, caudate or putamen and associated temporal cortical regions (Li et al., 2010b; Baeken & De Raedt, 2011; Walsh & Cowey, 2000). In terms of neurotransmitters, dopamine plays an important role in EF and Landau et al. documented that TMS-induced prefrontal–striatal network modulation was consistent with the bilateral involvement of striatal dopaminergic function in relation to a working memory task (Landau et al., 2009) and this was re-confirmed by a PET study (Monchi et al., 2006).

In terms of dosage of TBS, a dose-dependent anti-depressant effect has been suggested (i.e. right prefrontal continuous TBS: 3600 pulses/day > 1200 pulses/day) by an open-labeled study (Chistyakov et al., 2010), and recently the author also demonstrated a double-blind, sham controlled study by using 3600 continuous stimuli at right prefrontal cortex (Chistyakov et al., 2015). But some studies investigating TBS's effects on motor cortex reported that TBS-induced plasticity cannot be enhanced simply by prolonging the stimulation duration. Gamboa et al. observed some interesting findings that when stimulating for too long, the after-effects were reversed (Gamboa et al., 2010). Gentner et al. also found that application of cTBS for a duration of 20 s (cTBS300) facilitated subsequently evoked motor potentials (MEP) recorded from APB muscle, but application of cTBS for a duration of 40 s (cTBS300) depressed MEP-size (Gentner et al., 2008). Therefore, whether TBS's antidepressant effects are dose-dependent remain elusive and warrant further investigations.

There were some limitations in our study. First, the facilitation seen appeared to result from a direct effect of real TBS on the DLPFC area, but non-specific effects of TBS such as acoustic cues and skin sensations should also be considered. Terao et al. found that the effect of TMS in shortening reaction times could be explained from the nonspecific intersensory facilitation (i.e.: audible clicking of the TMS coil) (Terao et al., 1997). However, the results in the present study are unlikely to be explained by intersensory facilitation because similar acoustic and vibration cues were also present in the active and sham groups. Second, the 10th session of stimulation may immediately influence our post-TBS executive evaluation. Hence, we arranged the evaluation 1 h later after the 10th session had been finished. From the different WCST performances of responders and non-responders after the 10th session of TBS, and in particular in Group B, the cumulative effect of synaptic plasticity over 10 days may still play more of a role more than the final stimulation. Third, in our study, we recruited 60 participants, but the sample size was still relatively small. Further large-scale double-blind studies are warranted..

5. Conclusion

To our knowledge, this was the first double blind, sham-controlled study investigating the cognitive effects of TBS in different stimulated protocols on patients with medication-resistant major depressive disorder. Our findings revealed that left prefrontal iTBS, but not right prefrontal cTBS or a combination of both, seems to be the best parameter for TBS in treating medication-resistant depression.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.pnpbp.2015.11.009.

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Declaration of interest

The authors have no financial interests or conflicts of interest to declare in relation to the content of this paper.

Contributors

Chih-Ming, Cheng finished the manuscript, data analyzing and performed the tbs; Mu-Hong, Chen also performed the tbs and data analyzing; Chi-Hung Juan, Chi-Fu Chang, and Hsin Jie Lu all designed the cognitive examination and performing. Tung-Ping Su, Ying-Chiao Lee, and Cheng-Ta Li recruited and rated patients.

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