doi:10.1093/brain/awx379 BRAIN 2018: 141; 1–5 | e18

BRAIN
A JOURNAL OF NEUROLOGY

LETTER TO THE EDITOR

High-dose spaced theta-burst TMS as a rapid-acting antidepressant in highly refractory depression

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Sir,

We read with enthusiasm the article by Li *et al.* (2014) that describes how a course of intermittent theta-burst stimulation (iTBS) over the left dorsolateral prefrontal cortex (L-DLPFC) produced robust antidepressant responses compared to sham stimulation in patients with treatment-refractory depression (Li *et al.*, 2014). TBS, a patterned form of repetitive transcranial magnetic stimulation (rTMS) modelled after endogenous hippocampal discharge patterns (Larson and Lynch, 1986; Huang *et al.*, 2005), has been shown to be more efficient than standard rTMS in modulating cortical excitability (Cárdenas-Morales *et al.*, 2009). Preliminary results indicate non-inferiority of 600 pulses/day of iTBS versus 3000 pulses/day of conventional rTMS in treating depression (Blumberger *et al.*, 2017). Li *et al.* found that iTBS in highly refractory depression led to a mean 33% reduction in the 17-item Hamilton Depression Rating Scale (HDRS17) (Li *et al.*, 2014), and degree of refractoriness predicted reduced efficacy (Li *et al.*, 2014). Higher refractoriness may require more rTMS pulses to produce an antidepressant response, which in turn would necessitate more rTMS sessions per acute course (Yip *et al.*, 2017). Multiple spaced TBS sessions can be applied over a day with selected time intervals between sessions in an effort to accelerate the onset of effect, thereby also reducing the number of days required to complete an acute course (Cazzoli *et al.*, 2012). To begin testing this hypothesis, we conducted an open-label trial of spaced iTBS for the treatment of depression in six patients with the highest level of treatment-refractoriness.

Eligible participants were 21–70 years of age and had major depressive disorder or bipolar II disorder as diagnosed by the Structured Clinical Interview for DSM-5. Participants were required to meet criteria for the highest non-psychotic treatment-refractoriness on the Maudsley Staging Method (MSM, 14/15) (Fekadu *et al.*, 2009) and have a baseline total score of $\geqslant$20 on the HDRS17 (Hamilton, 1960) in the current episode. Participants must have received an FDA-approved rTMS treatment course with $\geqslant$60 000 pulses of deep rTMS (Levkovitz *et al.*, 2015) or $\geqslant$90 000 pulses of conventional rTMS over L-DLPFC and have failed to meet responder criteria (Lisanby *et al.*, 2009). Participants also were required to

Advance Access publication February 5, 2018

have failed to respond to an acute course of electroconvulsive therapy and to meet deep brain stimulation inclusion criteria (Filkowski *et al.*, 2016). Participants were excluded if they had a history of a psychotic disorder, substance use disorder, major systemic illness, lesional neurological disorder, or brain implant. We recruited six participants for this trial. Full written informed consent was obtained for all participants. The study was conducted according to the Declaration of Helsinki and approved by the Stanford Institutional Review Board. All participants were profoundly functionally impaired—either unemployed, on disability, or with significantly reduced workloads due to depressive symptoms. Participant demographics, prior treatments, and baseline measures are included in Table 1.

All participants completed pre-/post-treatment 8-min resting state functional connectivity and structural T_1-weighted MRI scans. For the targeting (pre-) scan, a hierarchical clustering algorithm (Drysdale *et al.*, 2017) was applied to each participant's resting state scan to identify personalized functional subregions within both the L-DLPFC and subcallosal cingulate (SCC) (Fox *et al.*, 2012). The L-DLPFC functional subregion with the strongest anti-correlation with SCC regions was selected as the stimulation target. This L-DLPFC functional target was then localized for each participant using the Localite Neuronavigation System. Participants were then treated with open-label spaced iTBS with 1800 pulses per session at 90% resting motor threshold and depth adjustment to the personalized functional target (Stokes *et al.*, 2005). Each session lasted 10 min followed by a 50-min intersession interval. Our iTBS pulse parameters were identical to those used by Li *et al.* (3-pulse 50-Hz bursts at 5-Hz for 2-s trains, with trains every 10 s). Ten sessions were applied per day (18 000 pulses/day) for five consecutive days (90 000 total pulses) using a Magventure Magpro X100 system. Depression severity was measured with the HDRS17 at baseline, immediately after the final session, and at 2 and 4 weeks follow-up.

All participants tolerated the therapy with no major adverse events. Participant 5 stopped treatment after completing Day 4 (receiving 72 000 pulses) due to perceived lack of effect, but followed through with measures and is included in all results. See Table 1 for depression ratings. There was a mean 76% reduction in HDRS17 from 28.8 ± 6.0 (mean $\pm$ standard deviation) at baseline to 7 ± 4.7 after the final session [repeated ANOVA, $F(2,10) = 19.58$, $P < 0.001$]. Five of six participants qualified as responders ($\geqslant$50% decrease in the HDRS17), and four participants were in full remission (HDRS17 $\leqslant$ 7) from depression by the final treatment session. At the 2-week follow-up visit, two participants remained responders, and there was a persistent 33% reduction on the HDRS17 (Dunnett's test, $P < 0.05$) across all six participants. At the 4-week time point, all participants no longer met responder criteria. Of note, Participant 5 who did not acutely respond to the treatment was later found to have obsessive-compulsive disorder (Yale-Brown Obsessive Compulsive Scale of 20) as his long-standing primary diagnosis, which he did not disclose at study entry. L-DLPFC is an ineffective therapeutic target for OCD (Berlim *et al.*, 2013) and an alternative target is required (Dunlop *et al.*, 2016).

Pre- and post-treatment neuropsychological testing data were available for five participants. Using non-parametric *t*-tests, performance at post-test either remained unchanged or improved in working memory, executive function, verbal learning and verbal memory domains. One participant had a transient visual memory decrement that renormalized on repeat testing. Five of six participants demonstrated an increased magnitude in anti-correlation between the functional subregions of the L-DLPFC and SCC after iTBS (Fig. 1). A participant with comorbid Parkinson's disease (Participant 3) taking levodopa demonstrated a reduction in anti-correlation magnitude, which may be due to altered functional connectivity in depressed patients with Parkinson's disease (Wei *et al.*, 2017). If this participant is excluded, the change in functional connectivity is significant [$t(4) = -3.024$, $P < 0.05$]. If included, the change in functional connectivity is not significant. A separate analysis of whole brain connectivity changes showed similar findings. Individual participants functional connectivity maps (Fisher's R-Z transformed) displayed increasing anti-correlations after iTBS in many SCC voxels (see Fig. 1A for representative participant). The paired *t*-test values of these iTBS-associated changes ranged from -2.18 to -7.62 but did not survive multiple comparisons corrections.

This work provides preliminary evidence for treatment of highly refractory depression with high-dose spaced iTBS. It was previously thought that depression at this level required invasive neuromodulation (Bergfeld *et al.*, 2016) because these interventions deliver constant stimulation (Williams *et al.*, 2016). Our study is limited by small sample size and lack of a sham control group; however, individuals with high refractoriness, such as those included in this study, have been previously shown to have no response to sham TBS (Li *et al.*, 2014). An additional new observation is that application of 18 000 pulses of patterned iTBS over 10 sessions separated by 50-min intersession intervals applied across a single day is preliminarily safe. This is the first study to our knowledge that reports this quantity of rTMS pulses applied to a human brain in one day. Although Li *et al.* used identical pulse parameters, the maximum number of iTBS pulses was limited to 1800 per day. Further, the total number of iTBS pulses delivered over the 2-week treatment was 18 000, compared to the 90 000 delivered over 5 days in the current study. Given the efficacy of this iTBS protocol with a mean 76% reduction in HDRS17 scores and response in five of six participants, this suggests the possibility that treatment-refractory depression non-responsive to stimulation of L-DLPFC may be a result of under-dosing (Li *et al.*, 2014; Yip *et al.*, 2017). Individuals with highly refractory depression may require more TMS pulses in a given day (Li *et al.*, 2014) and/or more total pulses (Yip *et al.*, 2017) than individuals with mild-moderate treatment-refractory depression.

Table 1 Participant demographics, prior treatments, baseline measures, and results

	Participant ID						Group
	1	2	3	4	5	6	
General characteristics							
Gender	M	F	F	F	M	F	4 F/2 M
Diagnosis at entry	MDD	BPAD Depressed	MDD	MDD	MDD[b]	MDD	5 MDD/1 BPAD
Age at treatment	69	53	66	47	63	38	56 (±12.1)
Education (years)	14	15	16	19	19	22	17.5 (±3.0)
Unemployed/functionally disabled	Y	Y	Y	Y	Y[a]	Y	All
Psychiatric history							
Age at MDD onset	32	18	20	18	33	23	24 (±6.8)
Length of illness (years)	37	35	46	29	30	15	32 (±10.3)
Current depressive apisode (years)	27	15	9	15	8	15	14.8 (±6.8)
Family history of MDD	Y	Y	Y	N	Y	N	4 Y/2 N
Psychiatric hospitalizations	0	5	1	0	2	7	2.5 (±2.9)
Treatment resistance							
Maudsley Staging Method	14	14	14	14	14	14	14
Thase and Rush Staging Method	5	5	5	5	5	5	5
Previous brain stimulation therapy failure							
VNS	Y	N	N	N	N	N	1 Y/5 N
ECT (courses)	1	2	1	1	1	1	1.2 (±0.4)
Right unilateral (total sessions)	0	12	12	10	15	0	8.2 (±6.5)
Bilateral (total sessions)	20	28	28	0	18	16	18.3 (±10.3)
TMS (courses)	2	1	2	2	1	2	1.7 (±0.5)
TMS (average sessions per course)	26	37	39.5	30.5	25	25	30.5 (±6.4)
DBS consultation	Y	N	N	Y	Y	Y	4 Y/2 N
Psychotherapy failure	Y	Y	Y	Y	Y	Y	All
Ketamine failure	Y	N	N	Y	Y	Y	4 Y/2 N
Baseline clinical assessments							
HRSD-17	34	26	29	27	20	37	28.8 (±6.0)
HRSD-6	17	15	15	15	14	20	16 2.2
MADRS	43	36	40	39	29	55	40.3 (±8.6)
BDI-II SR	39	64	34	47	22	53	43.2 (±14.8)
CGI-S	7	7	7	7	7	7	7
Immediate post-stimulation clinical assessments							
HRSD-17	3	5	5	8	16[c]	5	7 (±4.7)
HRSD-6	1	2	2	3	12[c]	0	3.3 (±4.4)
MADRS	1	0	1	6	19[c]	9	6 (±7.3)
BDI-II SR	7	3	8	19	23[c]	12	12 (±7.6)
CGI-S	1	1	1	1	5[c]	1	1.7 (±1.6)
Two weeks post-stimulation clinical assessments							
HRSD-17	17	26	14	18	14	27	19.3 (±5.8)
HRSD-6	9	15	7	9	9	16	10.8 (±3.7)
MADRS	21	35	13	29	38	19	25.8 (±9.8)
BDI-II SR	21	54	16	27	17	47	30.3 (±16.2)
CGI-S	4	7	5	4	4	6	5 (±1.3)
Four weeks post-stimulation clinical assessments							
HRSD-17	25	N/A[d]	20	26	18	31	24 (±5.1)
HRSD-6	12	N/A[d]	10	13	13	18	13.2 (±2.9)
MADRS	38	N/A[d]	21	40	25	43	33.4 (±9.8)
BDI-II SR	33	N/A[d]	23	47	21	54	35.6 (±14.5)
CGI-S	6	N/A[d]	7	7	5	7	6.4 (±0.9)

BDI-II SR = Beck Depression Inventory Self Report; BPAD = Bipolar Affective Disorder; CGI-S = Clinical Global Impression - Severity Scale; DBS = deep brain stimulation; ECT = electroconvulsive therapy; HDRS-17 = Hamilton Rating Scale for Depression 17 point; MADRS = Montgomery-Asberg Depression Rating Scale; N/A = not applicable; MDD = Major Depressive Disorder; TMS = transcranial magnetic stimulation; VNS = vagus nerve stimulation.

[a]This subject previously acquired a doctoral degree and was employed as a professional; currently works part time in service industry.

[b]At time of enrolment, this subject carried a MDD diagnosis, but was subsequently found to have OCD and withdrew from the study.

[c]This subject withdrew from the study following 40 of 50 stimulation sessions.

[d]This subject received retreatment prior to this time point.

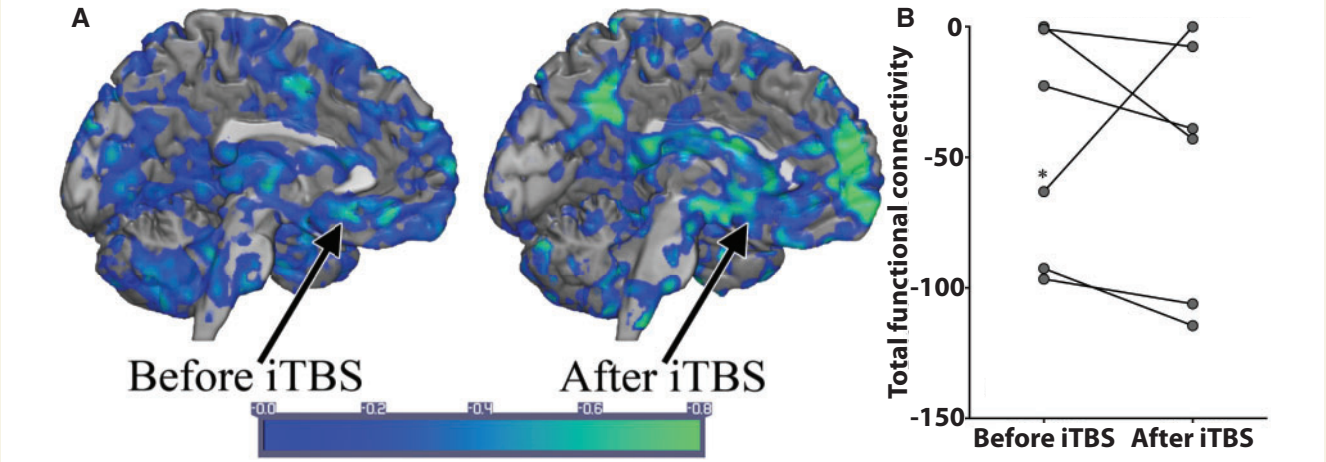

Figure 1 Personalized and targeted iTBS establishes new anti-correlations between L-DLPFC and SCC. (**A**) A representative participant's Fisher's R-Z transform map of anti-correlations between the L-DLPFC before and after iTBS. The arrow indicates the approximate location of SCC. (**B**) Total anti-correlation functional connectivity between L-DLPFC and SCC increases in magnitude after iTBS in five of six participants. Negative numbers on the vertical axis indicate the magnitude of anti-correlation. ∗The one participant in which the anticorrelation was reduced in magnitude had a diagnosis of Parkinson's disease and was taking levodopa.

Additionally, in contrast to ⩾24-h spacing of TBS sessions in Li *et al.*, this study implemented 50-min intersession intervals, which may enhance the efficacy of TBS. This approach was modelled after animal studies that showed hour-long intervals may be optimal for producing long term potentiation via TBS (Kramár *et al.*, 2012; Lynch *et al.*, 2013). In addition to optimization of the iTBS parameters, we used a personalized targeting approach based on identifying functional subunits of the L-DLPFC that are anti-correlated with SCC. This approach was developed as the functional connectivity of TMS targets has been shown to be related to efficacy in studies of motor physiology (Nettekoven *et al.*, 2015); furthermore, the functional connectivity of SCC is associated with severity of treatment-refractory depression (Greicius *et al.*, 2007) and stimulation sites within L-DLPFC with the highest anticorrelation with SCC are associated with greater efficacy (Fox *et al.*, 2012, 2014). In line with these reports, we found strengthened anti-correlations between DLPFC and SCC in five of six patients after TBS.

Optimized iTBS parameters with individual-level functional targeting described herein may offer a non-invasive and rapid approach that is effective even in cases of highly treatment-refractory depression. Larger controlled trials are underway to further test this hypothesis.

Funding

This work was supported by the Avy L. and Robert L. Miller Foundation, Stanford Psychiatry Chairman's Small Grant, Stanford CNI Innovation Award, NIH T32 035165, NIH UL1 TR001085, Stanford Medical Scholars Research Scholarship, NARSAD Young Investigator Award and the Gordie Brookstone Fund.

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