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## Brief Report

# iTBS to Relieve Depression and Executive Dysfunction in Older Adults: An Open Label Study

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## ABSTRACT

**Background:** Executive Function Deficits (EFD) accompany depression and are associated with poor outcomes in older adults. We examined whether Intermittent Theta Burst Stimulation (iTBS) could improve depression with EFD. **Methods:** Thirteen geriatric patients with depression and EFD were enrolled. Open label iTBS was delivered bilaterally over the dorso-lateral-prefrontal-cortex for four weeks. **Results:** Montgomery Asberg Depression Scale scores improved significantly from baseline to treatment-end, mean change in score = 11.82 points, 95% CI = 8.3, 15.4. The Flanker Inhibitory control and attention test showed significant improvement in executive function from baseline to treatment-end, mean change in score = -7.73, 95% CI (-13.54, -1.92). Side effects included twitching in facial muscles (n = 11), headaches (n = 10) and stimulation discomfort (n = 4). **Limitations:** Small sample size and lack of a sham comparator. **Conclusion:** iTBS improved depression with EFD in older adults. Side effects appeared higher than in previous iTBS studies. (Am J Geriatr Psychiatry 2020; ■■■:■■■-■■■)

## INTRODUCTION

Late Life Depression (LLD) is characterized by deficits in several cognitive domains, particularly

Executive Function Deficits (EFD). Affected executive domains include impulse inhibition, cognitive flexibility, planning and organization, semantic fluency and selective attention.<sup>1</sup> EFD predicts antidepressant treatment resistance, increased disability,<sup>2</sup> poor quality of life and an increased risk for suicide.<sup>3</sup> Treatment

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options for LLD with EFD remain limited, because of poor response to antidepressants, and psychotherapy interventions targeting this problem are not widely available.<sup>3</sup>

Structural alterations in brain regions underlying the executive and broader cognitive impairments found in LLD include volumetric changes affecting grey matter of fronto-striatal and limbic circuits and microstructural changes in white matter, which have been attributed to vascular disease affecting these circuits.<sup>4</sup> From a brain-systems perspective, network-dysfunction may be an underlying mechanism contributing to EFD in LLD. Findings of low resting state functional connectivity within the Cognitive Control Network associated with EFD support this premise.<sup>3</sup>

Neuromodulation interventions targeting specific brain circuits could be a potential treatment for LLD with EFD. Intermittent Theta Burst Stimulation (iTBS) is a newly FDA-approved Transcranial Magnetic Stimulation (TMS) paradigm to treat depression.<sup>5</sup> iTBS delivers magnetic pulses in “bursts” of 3 stimuli at 50 Hz repeated at 5 Hz. This excitatory TMS paradigm can enhance neuroplasticity via long-term potentiation<sup>5,6</sup>. Studies using iTBS in healthy mixed-aged adults suggested task-dependent modulation of executive function with greater effects observed with older age.<sup>6</sup> A significant advantage of iTBS is the very short 3 minutes treatment time in relation to conventional rTMS which last 26 minutes.<sup>5</sup>

Motivated by iTBS’s potential to enhance executive function and its efficiency, we sought to examine the feasibility and tolerability of bilateral iTBS over the Dorso-lateral prefrontal cortex (DLPFC) in geriatric patients with depression and co-occurring EFD. We targeted the DLPFC, because it is a key structure orchestrating executive control and a main node of the Cognitive Control Network, which subserves executive control.<sup>7</sup> iTBS was chosen on the premise that excitatory stimulation could enhance neuroplasticity in this system.<sup>5,6</sup> Stimulation was delivered bilaterally because brain systems supporting executive control are bilaterally distributed.<sup>8</sup> Moreover, given our focus on executive dysfunction, our choice of paradigm was supported by previous work by Barr and colleagues demonstrating that high-frequency (excitatory) bilateral stimulation over the DLPFC improved working memory.<sup>9,10</sup> We hypothesized that iTBS would significantly improve both depression and executive function in older adults. Finally, we

explored whether change in depressive symptoms with iTBS correlated with change in executive function.

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## METHODS

This prospective-open-label study was conducted from December 2016 to October of 2018. All participants provided informed consent according to Institutional Review Board proceedings. We recruited participants for a study of iTBS for depression and EFD using advertisements (social media and print), data bases of research volunteers and referrals from geriatric psychiatry and TMS clinical and research services at Washington University. Participants were aged 60–85 years old with a diagnosis of major depressive disorder, single or recurrent, diagnosed using the Structured Clinical Interview for DSM IV,<sup>11</sup> and scored at least 15 on the Montgomery Asberg Depression rating scale (MADRS).<sup>12</sup> Participants had to demonstrate EFD as evidenced by either: a) scoring between 0 and 2 Standard Deviations (SD) below the mean normative score on the average of the NIH Toolbox executive measures<sup>13</sup>: Flanker Inhibitory Control and Attention Test (Flanker) and the Dimensional Sort Card Test (DCCS) (approximate between 70 and 100); b) Discrepancy of at least 10 points between the average of the Picture Vocabulary score and the reading Recognition Test score and the average of the Flanker and the DCCS; c) Frontal Systems Behavior Scale (FrSBe)<sup>14</sup> T scores above 60 (indicative of impairment) and  $\geq 10$  points (1 SD) above participant’s premorbid (predepression) scores. Overall, inclusion criteria for EFD were broad. We used criterion b in an effort to add to the specificity of the EFD as opposed to more global cognitive deficits. Criterion c was aimed to capture EFD emerging with or concurrent with depression. Exclusion criteria were: dementia diagnosis; score  $< 24$  on the Montreal Cognitive Assessment<sup>15</sup> during the screening visit; bipolar or psychotic disorder; alcohol or substance use disorder within 6 months; active suicidal ideation; history of receiving TMS or nonresponse to electroconvulsive therapy; antidepressant therapy changes or recent initiation of psychotherapy or taking cognitive enhancers or stimulant medications; and contraindications to iTBS (i.e., presence of metal in the head, history of seizures, major head trauma). iTBS consisting

of three 50Hz stimuli, repeated at 5 Hz, 2 seconds on, 8 seconds off, 600 pulses (190 seconds duration)<sup>5</sup> was delivered sequentially first over the left DLPFC and then the right DLPFC using a Magpro R30 stimulator with a B65 figure-of-eight cool-coil. We used the Beam F3 method to localize the DLPFC.<sup>16</sup> To localize the right DLPFC we used the Beam F3 coordinates on the right hemisphere. A total of 20 iTBS sessions were administered five-days a week over four weeks. The Resting Motor Threshold (RMT) was determined for each left and right hemisphere. Stimulation intensity was rapidly titrated upward to achieve 120% of the observed RMT. Although we did not use structural scans to assess for prefrontal atrophy, our stimulation intensity was chosen based on previous work by Nahas and colleagues demonstrating that a mean of 114% (range 103%–141%) RMT intensity is needed to overcome prefrontal atrophy in the elderly.<sup>17</sup> However, this approach does not account for individual differences in scalp-to-cortex distance.

The depression primary-outcome was the change in MADRS scores from baseline to the end of the intervention (4 weeks). The Executive primary-outcome was the change from baseline to the end of iTBS in the NIH Tool Box executive measures: The Flanker test (measures visuospatial inhibitory attention) and the DCCS (measures cognitive flexibility). Because working memory (ability to acquire, transiently maintain and timely manipulate information) supports executive function we also examined performance on the List Sorting Working Memory test.<sup>13</sup> The executive secondary outcome was the change in the executive subscale of the self-reported FrSBe measured at

baseline and postintervention. This FrSBe executive-sub-scale consists of 17 questions describing dysexecutive-behavior.

We used paired t test to examine changes in depression and executive variables from baseline to post-iTBS. We examined the association between degree of mood improvement and degree of improvement in executive function using Spearman's rank correlation coefficients. We used IBM SPSS version 24 for all analyses.

## RESULTS

Of 13 enrolled participants one withdrew consent prior to starting the intervention (not analyzed) and one participant withdrew after three iTBS sessions. [Supplementary Table 1](#) shows demographic and clinical characteristics of study participants. Briefly, most participants were female, with a mean of 15.4 years of education. All participants had recurrent depression, and generalized anxiety disorder was comorbid in 41.7% (5 of 12) of cases. Most participants, 83% (10 of 12) were on stable doses of antidepressants which remained unchanged throughout the study. One subject initiated an atypical antipsychotic at study session 18. Inclusion criteria for EFD were broad, [supplementary Table 2](#) shows EFD criteria met by each participant. A total of 67% (8 of 12) subjects met criteria a, 83% (10 of 12) met criteria b and 58% (7 of 12) met criteria c.

[Table 1](#) shows mood and executive scores from baseline to 4 weeks post- iTBS. The group's average

**TABLE 1. Mood and Executive Function Improvement Post iTBS (n = 11)**

Outcome Variable	Baseline Mean (SD)	Week 4 Mean (SD)	Mean Change Score (95% CI)	T <sup>a</sup>	p
MADRS	27.73 (8.21)	15.91 (10.05)	11.82 [8.3, 15.4]	7.43	<0.001
Flanker Inhibitory Control	91.00 (6.97)	98.73 (12.8)	-7.73 [-13.54, -1.92]	-2.96	0.01
Dimensional Change Card Sort	104.27 (11.25)	105.00 (17.16)	-.73 [-10.90, 9.45]	-0.16	0.88
Working Memory	100.82 (11.1)	105.09 (10.29)	-4.27 [-13.25, 4.70]	-1.06	0.35
Self-report Executive FrSBe	48.55 (9.42)	39.36 (8.48)	9.18 [3.83, 14.53]	3.83	0.003
Mixing up a sequence <sup>b</sup>	3.55 (0.82)	2.73 (1.19)	.818 [0.09, 1.54]	2.52	0.03
Repeat mistakes <sup>b</sup>	3.09 (1.14)	1.91 (0.70)	1.18 [0.52, 1.84]	3.99	0.003
Is disorganized <sup>b</sup>	3.73 (1.01)	3.09 (0.94)	.64 [0.18, 1.09]	3.13	0.01
Poor judgement <sup>b</sup>	3.09 (0.94)	2.00 (1.18)	1.09 [0.27, 1.91]	2.96	0.01
Thinking before acting <sup>b,c</sup>	3.18 (0.98)	4.00 (0.45)	-.82 [-1.60, -0.03]	-2.32	0.04
Uses strategies to remember <sup>b,c</sup>	3.27 (1.19)	3.64 (1.36)	-.36 [-0.70, -0.03]	2.39	0.04

<sup>a</sup> Paired sample t test with 10 degrees of freedom.

<sup>b</sup> Individual items on the FrsBe executive subscale with p < 0.05.

<sup>c</sup> Reverse scored item. *Abbreviations:* SD, standard deviation; CI, confidence interval; MADRS, Montgomery-Asberg Depression Scale; FrSBe, Frontal Systems Behavior Scale.

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MADRS score decreased significantly from baseline, Mean (M) = 27.73, SD = 8.21 to treatment-end M = 15.91, SD = 10.05,  $t(10) = 7.43$  ( $p < 0.001$ ) denoting improvement. One-third (4 of 12) of the participants were responders ( $\geq 50\%$  decrease in MADRS scores) and one-third (4 of 12) were remitters (MADRS scores  $\leq 10$ ). Two executive measures significantly improved: Flanker scores increased from baseline M = 91.00, SD = 6.97 to treatment-end M = 98.73, SD = 12.8,  $t(10) = 2.96$ ,  $p = 0.01$  and FrSBe executive-subscale showed significant decrease in dysexecutive-behavior from baseline M = 48.55, SD = 9.43 to treatment-end M = 39.36, SD = 8.48,  $t(10) = 3.83$ ,  $p = 0.003$ .

Improvement in MADRS scores was positively albeit nonsignificantly related to improvement in the Flanker  $r_s = .32$ ,  $p = 0.34$ . Improvement in mood was not correlated with improvement in any other executive measures (statistics available upon request).

Common side effects were twitching in facial muscles during the stimulation 91% ( $n = 11$ ), headaches 83% ( $n = 10$ ) and pain or discomfort at the stimulation site and face 33% ( $n = 4$ ). No serious adverse events occurred. One participant withdrew because unable to tolerate the stimulation intensity (8.3% drop out rate).

## DISCUSSION

In this study, older adults undergoing iTBS over bilateral DLPFC experienced both, improvements in depression and executive function. Because our emphasis on EFD, our target differed from the conventional DLPFC antidepressant target namely, left-sided (excitatory) or combination of left-sided (excitatory) plus right-sided (inhibitory) TMS.<sup>18</sup> Nonetheless, we found depression improvement with a significant decrease in MADRS depression scores from baseline. Similarly, our remission rate of 33.3% compared favorably with a 32% remission rate found in the THREE-D study using iTBS, but remains inferior to the 40% remission rate reported with bilateral deep-TMS targeting ventrolateral and dorsolateral prefrontal regions, in older adults.<sup>19</sup>

Among the executive measures the flanker improved significantly post-iTBS. This test examines a person's ability to focus attention to relevant stimuli, while inhibiting attention from irrelevant stimuli. Impaired inhibition of negative stimuli may be a feature of depression. For example, Zetsche and

colleagues demonstrated reduced interference control of negative words in depressed patients, using an emotional Flanker task.<sup>20</sup> It is possible that bilateral stimulation over the DLPFC exerted effects on prefrontal brain systems involved in attentional processes including the fronto-parietal and/or cingulo-opercular networks.<sup>8</sup> Enhanced control over negative stimuli may have contributed to improvement in mood.

In tandem with executive function improvement on the psychometric testing, dysexecutive-behaviors significantly decreased, with the greatest improvement in behaviors involving sequencing, updating, organization, using judgment and problem solving, inhibition of impulses, planning and using organizational strategies. Because Dysexecutive-behaviors are associated with disability in LLD, lessening of these behaviors in this population is clinically meaningful.<sup>2</sup>

In terms of tolerability, our side effects rates are higher than previously reported, for example the THREE-D study had an incidence of headaches of 65% and a 70% rate of any side effect with unilateral iTBS. Despite a patient dropping out, our retention rate of 92% comports similarly to the 94% retention rate for those receiving iTBS in the THREE-D study. A more gradual titration to achieve the 120% required stimulation intensity could have resulted in better tolerability of our protocol.

Limitations of the study include: First, a small sample size and the lack of a sham or control group. Second, the selection of patients with depression and concurrent EFD may yield a nonrepresentative sample of candidate patients, because under real-world circumstances clinicians may recommend TMS treatment for patients with depression even in the absence of EFD. Third, inclusion criteria for EFD were relatively broad so as to be inclusive and enhance generalizability, though this could have introduced heterogeneity that may have impacted the outcomes. Last, changes in the NIH tool box executive measures could include practice effects which cannot be differentiated from the effects from iTBS. Therefore, results on iTBS's efficacy should be prudently interpreted and replicated with a control condition.

Nonetheless, this work informs on the feasibility and side effect profile of iTBS in geriatric patients and is a step towards testing a network-based treatment approach to LLD. We are currently investigating iTBS's mode of action using functional neuroimaging, under randomized-controlled conditions.

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## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.jagp.2020.03.001>.

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