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RESEARCH ARTICLE

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A pilot randomized sham controlled trial of bilateral iTBS for depression and executive function in older adults

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Abstract

Introduction: Executive function deficits (EFD) in late life depression (LLD) are associated with poor outcomes. Dysfunction of the cognitive control network (CCN) has been posited in the pathophysiology of LLD with EFD.

Methods: Seventeen older adults with depression and EFD were randomized to iTBS or sham for 6 weeks. Intervention was delivered bilaterally using a recognized connectivity target.

Results: A total of 89% (17/19) participants completed all study procedures. No serious adverse events occurred. Pre to post-intervention change in mean Montgomery-Asberg-depression scores was not different between iTBS or sham, $p = 0.33$. No significant group-by-time interaction for Montgomery-Asberg Depression rating scale scores ($F_{3, 44} = 0.51$; $p = 0.67$) was found. No significant differences were seen in the effects of time between the two groups on executive measures: Flanker scores ($F_{1, 14} = 0.02$, $p = 0.88$), Dimensional-change-card-sort scores $F_{1, 14} = 0.25$, $p = 0.63$, and working memory scores ($F_{1, 14} = 0.98$, $p = 0.34$). The Group-by-time interaction effect for functional connectivity (FC) within the Fronto-parietal-network was not significant ($F_{1, 14} = 0.36$, $p = 0.56$). No significant difference in the effect-of-time between the two groups was found on FC within the Cingulo-opercular-network ($F_{1, 14} = 0$, $p = 0.98$).

Conclusion: Bilateral iTBS is feasible in LLD. Preliminary results are unsupportive of efficacy on depression, executive function or target engagement of the CCN. A future Randomized clinical trial requires a larger sample size with stratification of cognitive and executive variables and refinement in the target engagement.

KEYWORDS

Cingulo opercular network, depression, executive dysfunction, Fronto parietal network, intermittent theta burst stimulation, late life depression, neuromodulation, older adults, resting state functional connectivity, transcranial magnetic stimulation

Key points

- ITBS over bilateral dorso-lateral-prefrontal-cortex in older adults with depression and executive function deficits was feasible and without serious side effects.

- This pilot study was unsupportive of the efficacy of bilateral iTBS for treating depression or executive function deficits (visuospatial inhibitory attention, cognitive flexibility, working memory) in older adults.
- Preliminary evidence showed no changes on resting state functional connectivity within the fronto-parietal-network, cingulo-opercular-network and default-mode-network, which are posited in the pathophysiology of late life depression.

1 | INTRODUCTION

Executive function deficits (EFD) including specialized cognitive processes involving inhibitory control, working memory and cognitive flexibility are a core problem in late life depression (LLD).[1–3] These deficits interfere with functioning and quality of life and are associated with poor depression prognosis including treatment resistance,[4,5] disability[6] and suicide.[7]

From a brain-systems perspective, disconnection in functional networks may be a common pathway that results in both persistent depressive symptoms and EFDs. The Cognitive Control Network (CCN) is a key top-town regulatory system supporting executive control[8] that includes both the Fronto-parietal- network and the Cingulo-opercular-network.[9,10] The Fronto-parietal-network initiates attentional control during tasks and the Cingulo-opercular-network allows maintenance of tasks and adjusting to error.[9,11] Regions forming the Fronto-parietal-network include the dorsolateral prefrontal cortex (DLPFC), inferior parietal lobule, dorsal frontal cortex, intraparietal sulcus and precuneus. The Cingulo-opercular-network includes the anterior prefrontal cortex, anterior insula/frontal operculum, dorsal anterior cingulate cortex/medial superior frontal cortex and thalamus.[9] Dysfunction of the CCN has been postulated as a core pathology in LLD associated with EFDs based on multiple lines of evidence: (1) Dysfunction affecting CCN regions has been linked to executive impairment in depression[12–14] (2) Low resting state functional MRI connectivity within the CCN[15,16] found in middle aged and older adults with depression has been associated with dysexecutive behavior and antidepressant resistance[15] and (3) Decreased activity in the DLPFC during cognitive tasks and decreased connectivity between the DLPFC and the dorsal anterior cingulate[4] has been described in LLD.

Non-invasive brain stimulation can address brain-circuit dysfunction via modulation of aberrant activity in local and connected brain regions implicated in neuropsychiatric disease.[17–19] Martin et al showed improvement in the executive set-shifting domain with Transcranial Magnetic Stimulation (TMS) compared to sham of a modest effect size.[20] Ilieva et al. demonstrated that the effect of left sided-TMS over the DLPFC on cognitive inhibition and cognitive flexibility increases with advancing age; and that executive improvement was associated with reduction in depressive symptoms.[21] iTBS was recently FDA-approved for depression[22] and is posited to modulate neuroplasticity.[23] iTBS′ pattern resembles theta rhythms (5–7 Hz) optimal for induction of long-term potentiation and implicated in learning and memory.[24] iTBS after-effects involve activity of the N-methyl-D-Aspartate receptor (NMDARs) affecting synaptic plasticity.[25] A recent systematic review, showed iTBS modulated executive control in a task-dependent manner.[26] We recently found improvements in both depression and EFD in older adults receiving iTBS over the DLPFC.[27] In that study iTBS was applied over bilateral DLPFC in order to affect bilaterally-distributed executive control systems.[28] Using this double-excitatory paradigm, we demonstrated behavioral change[27] but as that study included only clinical and neuropsychological measures, the mechanism of action of bilateral iTBS could not be tested and remains unknown.

Accordingly, we conducted a pilot randomized double blind controlled study to examine both the preliminary clinical effects and potential mechanisms of iTBS in older adults with depression and EFD. Using rsFMRI before and after a course of real or sham iTBS we probed whether iTBS modulates the CCN, improving brain connectivity within this network, and whether network engagement is associated with behavioral improvement. The objectives of the study were: (1) Evaluate feasibility to proceed to a definitive clinical trial, based on enrollment, retention and tolerability of the intervention and study procedures. (2) Examine preliminary efficacy of iTBS to improve depression and EFDs in older adults, whereby participants receiving iTBS will exhibit greater improvement in depression and EFDs than those on sham. (3) Probe whether iTBS modulates the CCN a main posited mechanism of EFDs in LLD. (4) Examine whether brain network- engagement is associated with clinical and behavioral improvement.

2 | METHODS

2.1 | Study design and participants

We conducted a randomized sham-controlled pilot study at Washington University medical center from April 2018 to April 2020 (ClinicalTrials.gov ID NCT03745768). We recruited outpatients from research volunteer databases, referrals from our geriatric and TMS clinical and research services and using printed and social media advertisements. All participants provided Informed consent following Institutional Review Board Committee guidelines.

Eligible participants were aged 60–85 years old, diagnosed with major depressive disorder, single or recurrent, using the Mini International Neuropsychiatric Interview Version 7.0 for DSM-5,[29] and scoring at least 15 on the Montgomery-Asberg Depression rating scale (MADRS).[30] EFDs were assessed using the NIH-Toolbox

executive measures and the Frontal Systems Behavioral Scale (FrSBe). We used age-corrected-standard-scores for the NIH-Toolbox measures,[31] which are standardized based on a normative sample so that mean = 100 and standard deviation (SD) = 15; this allows comparison of each study participant's scores versus a healthy population. Eligible participants had EFDs if they had any of the following: (a) scoring between 0 and 2 Standard Deviations (SD) below the mean normative score on the average of the Flanker Inhibitory Control and Attention Test (Flanker) and the Dimensional Change Card Sort Test (DCCS) NIH-Toolbox executive measures, for example, approximate average scores between 70 and 100; or, (b) At least 10 points difference between the average of the NIH-Toolbox Picture Vocabulary age-corrected-standard scores and the reading Recognition Test age- corrected- standard-score and the average of the Flanker and the DCCS. This difference helped to discriminate executive deficits from more global cognitive deficits; or, (c) FrSBe[32] T scores above 60 (indicative of impairment) and ≥10 points (1 SD) above the participant's reported pre-depression scores. Exclusion criteria included: diagnosis of dementia; Montreal Cognitive Assessment (MoCA)[33] score <22 indicative of moderate to severe cognitive impairment, although individuals with lower scores could be included per principal investigator's clinical judgment; bipolar or psychotic disorder; alcohol or substance use disorder within 6 months; active suicidal ideation (determined by study psychiatrist); previous TMS treatment, non-response to electroconvulsive therapy; recent initiation of psychotherapy; prescribed stimulants or cognitive enhancers medications; and contraindications to iTBS (presence of metal in the head, history of seizures, major head trauma, pacemaker). We limited concurrent benzodiazepine use to 2 mg/day lorazepam-equivalent and no anticonvulsants were permitted except for low-dose gabapentin (maximum 600 mg/day).

2.2 | Intervention

We used a Magpro R30 stimulator with a with a B-65 A/P active and sham coil (MagVenture A/S—Farum, Denmark). This coil has a symmetric identical design on both surfaces but it is shielded to reduce the magnetic field strength of a negligible level of <5% of the active field when flipped over the inactive face. At each session, iTBS (or sham) was delivered sequentially: first over the left DLPFC and then the right DLPFC, similar to our prior study.[27] A single run of iTBS was delivered using a triplet burst at 50 Hz, repeated at 5 Hz, 2 s on, 8 s off, 600 pulses (190 s duration).[22] The control group received sham intervention with the coil flipped over the inactive surface, with matching parameters and identical clicking noises. A total of 30 treatments (active or sham) were delivered 5-days a week over 6 weeks. Scalp sensations were masked using synchronized electrical current to the scalp via pre-gelled surface stimulation electrodes during both active and sham conditions. The TMS operator was blinded to the assignment of active versus sham conditions. Research software on the TMS device prompted the operator to "flip" the coil according to the subject's assignment preserving the blind.

Stimulation was delivered at 120% of the Resting Motor Threshold (RMT) according to FDA-approved stimulation intensity.[22,34] We used an adaptive titration protocol to increase stimulation to reach 120% of RMT intensity during the first five sessions. Details of stimulation titration and RMT determination in supplementary material.

Stimulation was targeted to the DLPFC a key node of the CCN, our network of interest for Executive Dysfunction.[8–10] Consistent with our goal to improve functional dysconnectivity, and based on prior research,[18] we chose a validated functional connectivity (FC) target within the DLPFC shown to predict antidepressant response to TMS.[35] The target was based on peak anticorrelation between the subgenual cingulate and the DLPFC which was derived from $n = 1000$ normative connectome data.[35] Montreal Neurological Institute (MNI) coordinates for the left DLPFC were $x, y, z = -42, 44, 30$ and MNI $x, y, z = 40, 44, 34$ for the right DLPFC (Michael D. Fox personal communication). Neuronavigation procedures are detailed in the supplementary material.

2.3 | Outcome measures

Feasibility outcomes were percentage of participants enrolled, participant's retention, tolerability and safety of the intervention and completion of study procedures.

Tolerability and safety were assessed by reporting of adverse events (AE). At each intervention session subjects were queried by the blinded iTBS operator about the occurrence of AE. A blinded investigator assessed AE relatedness to the intervention. Serious AE were those considered important medical events, leading to hospitalization or disability.

Preliminary efficacy in depression was measured by comparing the reduction in MADRS[30] scores pre-intervention to completion of 30 aggregate treatments in both active and sham groups. Pre-intervention and post-intervention MADRS scores were assessed within 2 weeks of study intervention. Response rate (50% MADRS score reduction from baseline) was assessed on an exploratory basis.

Preliminary efficacy for Executive dysfunction was the change in each of the three NIH-Toolbox executive measures from pre-to post-intervention (completion of 30 treatments): The Flanker Inhibitory Control and Attention test (measuring visuospatial inhibitory attention), the Dimensional Change Card Sort DCCS (measuring cognitive flexibility), and the List Sorting Working Memory test (measuring working memory).[31] Exploratory executive measures were the change in the self-reported FrSBe executive sub-scale (measuring dysexecutive behavior) and a semantic fluency test. For comparison purposes, we also examined the effect of the intervention on crystallized cognition measures from the NIH Toolbox Cognitive Battery including oral reading recognition and picture vocabulary, which were not expected to change with intervention.[31] Executive function was assessed within 2 weeks pre- and post-intervention.

Effects of iTBS on FC were examined by comparing resting state connectivity values for the Fronto-parietal-network and the Cingulo-

opercular-network pre- and post-intervention in both active and sham groups. Additionally, on an exploratory basis we examined the effects of iTBS on resting- state FC within the Default-mode-network using the same approach. The Default-mode-network is implicated in regulation of emotional processing in depression[36] and is thought to exhibit altered FC in LLD.[37,38]

A sample size of 20 completers (10 in each group) was chosen to demonstrate feasibility of the intervention and based on the resources available for the study. Randomization scheme is detailed in supplementary material.

2.4 | Functional MRI acquisition, processing and analysis

2.4.1 | Image acquisition

Images were acquired on a SIEMENS Prisma Fit 3T MRI scanner (Siemens Medical Solutions, Malvern, PA) equipped with a 32 Channel head coil at the Center for Clinical Imaging Research Washington University School of Medicine.

The imaging sequence included T1-weighted (MP-RAGE, TR = 2400, TR = 3.16, TI = 1000 ms; 1 × 1 × 1 mm voxels) and T2-weighted (TR = 3200, TE = 458 ms; 1 × 1 × 1 mm voxels) anatomical images and multi-echo BOLD (TR = 2960, TE = 15, 31.31, 47.62, 63.93 ms; 4 × 4 × 4 mm voxels; 4 runs of 140 frames each). Subjects were instructed to keep their head still during the scan and were shown a silent video of neutral content (underwater scenes) during the collection of the functional images.[39] Frame-wise Integrated Real-time MRI Monitoring provided feedback to subjects to minimize head motion during scans.[40] MRIs were collected within 2 weeks pre- and post-intervention.

2.4.2 | Image data analysis

Functional MRI data were processed following methods described by Raut et al.[41] Briefly, the preprocessing reduced slice and time dependent intensity artifacts and noise, standardized the whole brain intensity to mode value of 1000, corrected for within-run head movement, and registered the data to a standardized space using an Atlas generated from 208 subjects from the MEDEX study[39] which used an identical protocol on the same scanner model. Multi-echo data were analyzed by least squares fitting of the theoretical model defined in equation 1 in Poser et al.[42] The fitted data then were converted to synthetic T2*-weighted images evaluated at TE = 30 ms. Nuisance regression was performed using white matter and ventricle segmentation generated from FreeSurfer acquisition, the mean video BOLD response averaged over all participants was subtracted from each subject time series. Frame censoring was conducted using the DVARS measure.[43] Percentage of frames censored is presented in Supplementary Table S2. Using a subset of Seitzman's and colleagues 300 functionally defined Regions of Interest (ROIs),[44] the frame censored time series was sampled to generate pairwise temporal correlation values for each ROI pair. Supplementary Table S3 shows MNI coordinates of ROIs in each network. For each investigated network, Fronto-parietal, Cingulo-opercular and Default-mode- network, the within-network ROI-ROI correlations were averaged to generate a network mean correlation value.

2.5 | Statistical analysis

Continuous variables are presented as the mean (standard deviation). Variability in the demographic and clinical characteristics (continuous) are presented as the range (min, max). Categorical variables are presented as number (percentage), and comparison for proportion was done using the Chi-squared Test or Fisher's Exact Test. Pearson's correlation coefficients were used to analyze correlations between variables.

Missing data on pre-interventional MADRS and on the motor threshold variable were imputed using Last Observation Carried Forward (see Supplement Material). Pre-intervention MADRS collected at screen or baseline visit in closer proximity to the start of the intervention was used for analysis (see Supplement Material). Repeated measures ANOVA examined the effects of time on the primary depression, executive and connectivity measures between the active and sham groups. Change from baseline to post-intervention in the MADRS depression score (MADRS) was estimated and compared between the two treatment groups.

Cohen's d was used to determine effect sizes and 95% confidence intervals for the mean change differences between active and sham. Fisher's Exact Test examined differences between groups in AE.

Statistical significance was defined as a two-sided *p*-value less than 0.05. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

3 | RESULTS

3.1 | Feasibility of the intervention

Nineteen subjects out of thirty-seven (51%) assessed of eligibility in-person were enrolled and randomized in 24 months. Due to closures from the COVID-19 Pandemic the study was stooped early. Nine subjects randomized to sham and 10 to active iTBS, two subjects (active group) discontinued after the first session. Seventeen subjects were analyzed and completed all study procedures, 89% (17/19) retention. CONSORT diagram (Figure 1) shows the number of participants screened, assessed for eligibility, randomized, and completing the trial and assessed for objectives. Table 1 shows demographic and clinical variables for all study participants and by group. In summary, over 50% were women, mean (standard deviation) of age was 67 ± 5 years old, average participants had completed 16 ± 2 years of education. The duration of the current depressive

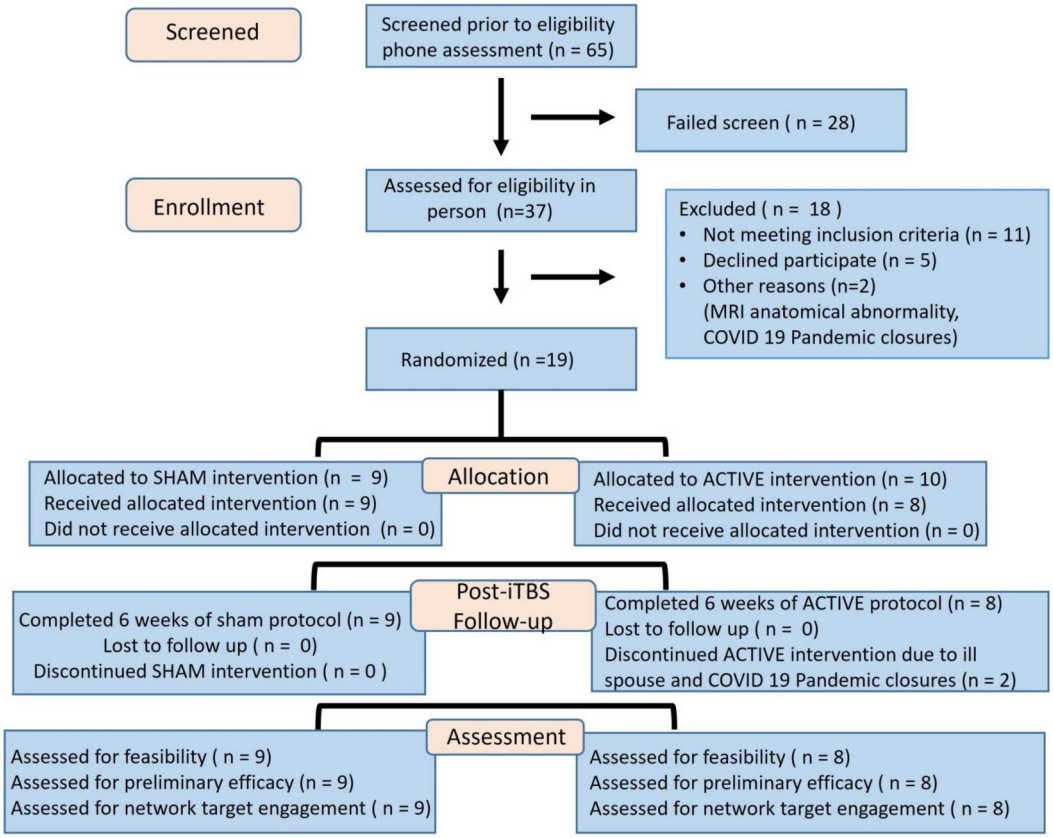

FIGURE 1 CONSORT diagram

episode was over 2 years (chronic) for the majority of participants. The mean (SD) of Cumulative Illness Rating Scale for Geriatrics CIRS-G score was 7 ± 4, showing a level of medical comorbidity (approximately three moderate medical conditions on average per participant) consistent with prior studies in LLD.[45] Sixty-five percent of participants had failed one previously adequate antidepressant trial per the Antidepressant Treatment History Form,[46] denoting low level of treatment resistance. Most participants, 76% (13/17) were on stable doses of antidepressants unchanged during the study except one (active group) who increased venlafaxine (75 to 150 mg/day) and one (sham group) who started alprazolam as sleep aid. Regarding global cognition, MoCA scores ranged from 20 to 30 denoting a range from normal to mild cognitive impairment.

3.2 | Safety and tolerability

No serious AE were reported in both groups. Adverse events experienced across groups included: headache, pressure in the head, twitching in the face, and other side effects. Other AEs included unpleasant sensation in the head, itching, pain and an upper respiratory illness. The two groups, active versus sham did not differ significantly in the occurrence of any of these AEs. Supplementary Table S1 details frequency of AEs by group.

Regarding tolerability, 88% (7/8) subjects receiving active stimulation achieved 120% of RMS by session 5 as stipulated in the protocol (three in session three and four in the first session). One subject (12%) in this group achieved 120% target intensity at the sixth session. See Table 1.

Blinding integrity was assessed upon completion of all study procedures and subjects were queried about suspected group assignment. In the active group 50% (4/8) guessed correctly; in the sham group 44.44% (4/9) guessed correctly.

3.3 | Preliminary efficacy of iTBS on depression and Executive function deficits

No significant difference in the change from pre to post-intervention in mean MADRS depression scores was detected between the groups ($p = 0.3322$). No significant group-by-time interaction effect for MADRS scores ($F_{3, 44} = 0.51$; $p = 0.67$) was found. A significant main effect of time was found for the MADRS ($F_{3, 44} = 18.89$; $p < 0.0001$), indicating that the mean scores decreased significantly across participants over time (Figure 2). The outcome of the MADRS was not found to be significantly different between the two groups ($F_{3, 44} = 3.55$; $p = 0.0778$). Exploratory outcomes showed the sham group had a higher response rate = 88.9% (8/9) than the active group = 37.5% (3/8), $p = 0.050$, Fisher's Exact Test.

No significant differences were seen in the effects of time between the two groups on any of the three executive measures: Flanker scores ($F_{1, 14} = 0.02$, $p = 0.88$), DCCS scores ($F_{1, 14} = 0.25$,

TABLE 1 Demographic and clinical characteristics of study population

Variable	Sham (n = 9)	Active (n = 8)	ALL (n = 17)
Demographic variables			
n (%) females	3 (33.3%)	6 (75%)	9 (52.9%)
Age (years, mean ± SD)	67 ± 5	66 ± 5	67 ± 5
Age (years min, max)	(63, 74)	(63, 74)	(63, 74)
Race			
White	8 (88.8%)	7 (88.0%)	15 (88.0%)
Black	1 (11.11%)	1 (12%)	2 (12.0%)
Education (years, mean ± SD)	16 ± 2	16 ± 3	16 ± 2
Education (years min, max)	(12, 18)	(12, 20)	(12, 20)
Living situation			
Alone, *n* (%)	5 (55.50%)	2 (25.00%)	7 (41.10%)
With spouse, *n* (%)	3 (33.30%)	3 (37.50%)	6 (35.20%)
Clinical variables			
Current major depressive episode, *n* (%)	9 (100%)	8 (100%)	17 (100%)
Length of the episode			
<2 years, *n* (%)	4 (44.44%)	3 (37.50%)	7 (41.18%)
≥2 years, *n* (%)	5 (55.56%)	5 (62.50%)	10 (58.82%)
Recurrent depression course, *n* (%)	8 (88.80%)	8 (100.0%)	16 (94.10%)
Comorbid generalized anxiety disorder, *n* (%)	2 (22.2%)	0 (0%)	2 (11.7%)
Previous history of ECT, *n* (%)	0 (0%)	1 (13%)	1 (6%)
History of prior psychiatric hospitalizations, *n* (%)	1 (11.1%)	0 (0%)	1 (5.8%)
Previous antidepressant treatment[a]			
One failed antidepressant	6 (66%)	5 (75%)	11 (65%)
Two failed antidepressants	0	1 (12.5%)	1 (6%)
Participants currently taking antidepressants	7 (77.8)	6 (75.00)	13 (76.47)
CIRS-G score (mean ± SD)	6 ± 4	9 ± 4	7 ± 4
MoCA score (mean ± SD)	25 ± 2	27 ± 3	26 ± 3
MoCA score (min, max values)	(20, 28)	(21, 30)	(20, 30)
Motor threshold intensity			
Recommended left motor threshold			
Prior to intervention (mean ± SD)	53.01 ± 10.17	50.5 ± 4.5	51.83 ± 7.90
Week 6 of intervention (mean ± SD)	53.88 ± 9.16	54.12 ± 6.83	54.00 ± 7.45
Motor threshold intensity			
Recommended right motor threshold			
Prior to intervention (mean ± SD)	52 ± 8.59	52.54 ± 6.52	52.25 ± 7.45
Week 6 of intervention (mean ± SD)	54.33 ± 7.40	54.00 ± 4.03	54.18 ± 5.88
Motor threshold target intensity			
Participants achieving 120% by session ≤5 *n* (%)	9 (100%)	7 (88%)	16 (94%)
Participants not achieving 120% by session ≤5 *n* (%)	0 (0.00%)	1 (12%)	1 (6%)

Abbreviations: CIRS-G, Cumulative illness Rating Scale for Geriatrics; MoCA, Montreal Cognitive Assessment.

[a]Adequate antidepressant trials had a score ≥3 on the Antidepressant history form (ATHF) denoting sufficient dose and duration (≥4 weeks).

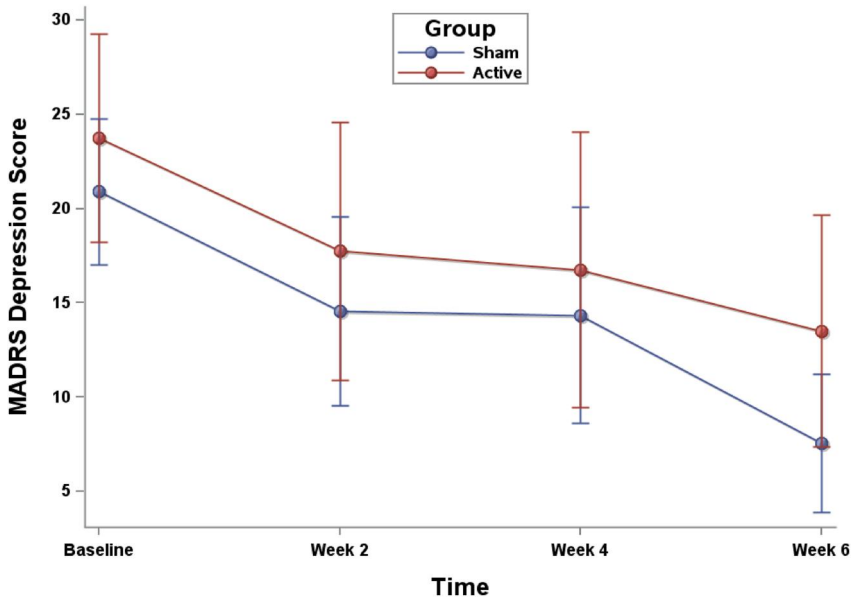

FIGURE 2 Change in depressive symptoms over time

$p = 0.63$), and working memory scores ($F_{1, 14} = 0.98$, $p = 0.34$). No significant effects of time or group were found.

The standardized difference in the mean change from baseline to post-intervention between the two groups was non-significant for either mood or executive measures (Table 2). Table 2 details baseline and post-intervention scores of depression and executive measures.

3.4 | Effects of iTBS on functional connectivity of Fronto-parietal network (FPN), Cingulo-opercular network (CON) and Default-mode-network (DMN)

The Group-by-time interaction effect for FC within the Fronto-parietal-network was not found to be significant ($F_{1, 14} = 0.36$, $p = 0.56$). A significant main-effect-of- group was found for Fronto-parietal-network ($F_{1, 16} = 6.86$, $p = 0.02$) indicating a significant difference in the mean Fronto-parietal-network connectivity between the two groups, driven by the higher Fronto-parietal-network connectivity means in the sham group (Figure 3).

No significant difference in the effect-of-time between the two groups was found on FC within the Cingulo-opercular-network ($F_{1, 14} = 0$, $p = 0.98$), Figure 4. Both main effects of group and time remained insignificant.

No significant difference in the effect-of-time between the two groups was found on FC within the Default-mode-network ($F_{1, 14} = 0.52$, $p = 0.48$). A significant main –effect-of -time was found on this measure ($F_{1, 14} = 6.54$; $p = 0.02$), indicating a significant increase in Default-mode-network connectivity means across participants over time (Supplementary Figure S1).

The standardized difference in the mean change from baseline to post-intervention between the two groups was non-significant for any of the brain connectivity measures (Table 2). Table 2 details pre and post-intervention mean and standard-deviation connectivity values.

3.5 | Association between brain network engagement and change in depression and Executive function deficits

Among all participants, we did not detect a significant correlation between changes in MADRS depression scores and changes in connectivity within Fronto-Parietal-Network ($r = -0.346$, $p = 0.17$), Cingulo-opercular-network ($r = 0.062$, p 0.81) or Default-mode-network ($r = -0.298$, $p = 0.25$).

Similarly, among all participants no correlation was found between change in executive measures and brain connectivity: Changes in flanker scores were not correlated with changes in connectivity within the Fronto-parietal-network ($r = 0.077$, $p = 0.769$), Cingulo-opercular-network ($r = -0.196$, $p = 0.450$), or Default-mode-network ($r = 0.002$, $p = 0.99$). Changes in the DCCS were not associated with connectivity within the Fronto-parietal-network ($r = 0.000$, $p = 0.99$), Cingulo-opercular-network ($r = -0.110$, p 0.67) or Default-mode-network ($r = 0.275$, $p = 0.27$). Changes in working memory were not associated with changes in connectivity within the Fronto-parietal-network ($r = 0.230$, $p = 0.38$); Cingulo-opercular-network ($r = -0.115$, $p = 0.66$) or Default-mode-network ($r = 0.309$, $p = 0.23$).

Supplementary Material and Supplementary Figure S2 shows exploratory outcomes on executive FrSBe scores, semantic fluency and other NIH cognitive measures.

4 | DISCUSSION

This pilot study examined the feasibility and explored the clinical and mechanistic effects of bilateral iTBS in older adults with depression and EFD.

Recruitment and enrollment were feasible, albeit recruitment was stopped due to the COVID-19 Pandemia. The majority (89%) of participants were retained and completed 6-weeks of extensive

TABLE 2 Baseline and post-intervention values for outcome measures and effect sizes

	Baseline mean and standard deviation		Post-intervention mean and standard deviation		
Outcome measure scores	**Sham $n = 9$**	**Active $n = 8$**	**Sham $n = 9$**	**Active $n = 8$**	**Effect size (95% CI)**
Depression					
MADRS depression scores	20.89 (3.89)	23.75 (5.52)	7.56 (3.68)	13.50 (6.14)	−1.77 (−3.96 to 0.43)
Executive function main outcomes					
Flanker score	91.44 (17.07)	94.75 (10.58)	90.67 (13.04)	93.38 (9.94)	0.08 (−8.57, 0.73)
Dimensional sort card test	102.89 (19.84)	106.5 (6.21)	104.55 (23.30)	105.5 (9.50)	0.20 (−0.80, 1.20)
List sorting working memory	98.89 (17.17)	100.88 (14.39)	105.89 (15.51)	101.75 (15.62)	0.37 (−0.41, 1.15)
Executive function exploratory outcomes					
Dysexecutive behaviors (Frsbe)	46 (8.12)	47.25 (9.62)	35.56 (7.37)	39.88 (9.43)	
Semantic fluency	19.44 (3.78)	19.5 (2.56)	19.33 (4.36)	21.38 (1.85)	
Crystallized cognition					
Oral reading recognition	118.11 (12.67)	120.13 (14.87)	118.11 (18.87)	125.12 (12.80)	
Picture vocabulary	113 (15.87)	110.25 (13.23)	112.43 (18.32)	110.5 (20.27)	
Brain connectivity					
Fronto parietal network	0.16 (0.06)	0.11 (0.02)	0.15 (0.05)	0.10 (0.03)	−0.034 (−0.98, 0.91)
Cingulo opercular network	0.18 (0.06)	0.15 (0.04)	0.19 (0.05)	0.16 (0.03)	−0.08 (−1.02, 0.87)
Default mode network	0.09 (0.02)	0.10 (0.41)	0.11 (0.04)	0.11 (0.05)	0.36 (0.28, 1.00)

Note: Effect size Cohen's *D*, 95% confidence interval shown for main outcome measures only.
Abbreviation: MADRS, Montgomery Asberg Depression Scale.

procedures including behavioral measures, fMRI scans and study intervention. Regarding safety, side effects were similar to those reported by unilateral iTBS and 10 Hz TMS in the THREE-D trial.[22] However, our criteria of reaching 120% of the RMT intensity within 5 days needs re-evaluation as inability to reach this goal could lead to under-dosing.

Preliminary results found no evidence of iTBS's efficacy for treating depression or EFD. In fact, both active and sham groups improved, but iTBS did not produce a greater improvement than sham after 6 weeks. Unexpectedly, the sham group had a higher response rate which is consistent with previously reported high placebo responses (up to 45%) in clinical trials of major depression[47–49] and supported by neurobiological mechanisms.[50,51] The lower pre-intervention depression scores in the sham group; the multidimensional sensory components (sound and electrical stimulation) mimicking stimulation of the sham and the relatively long 6-weeks duration of the intervention during which subjects may had had naturalistic improvement could had contributed to the observed placebo response.[48]

Examination of preliminary efficacy of iTBS on executive function showed no differences between groups on the Flanker and DCCS or on the working memory. Contrasting with previous report of high frequency (excitatory) bilateral TMS improving executive function in patients with schizophrenia.[52] Presently, the appropriate paradigm to enhance executive function in LLD remains uncertain, and a recent study using deep TMS did not induce changes in executive function in this population.

Regarding brain connectivity, we did not detect changes in FC in any of the brain networks posited in the pathophysiology of LLD. Further, we found no relationship between network changes and either depression or executive function changes. Although these preliminary results may be regarded as a failed or null test of network target engagement, two important factors may had led to undetectable FC changes: First, we were underpowered to detect group differences and second, FC does not consistently has a high test-retest reliability, at least for some brain regions and metrics[53]

Importantly, bilateral iTBS has not been previously studied for treating depression in younger or older adults. In contrast, the sequential bilateral approach of inhibitory stimulation (1 Hz) to the right DLPFC and excitatory stimulation (10 Hz) to the left DLPFC has demonstrated efficacy with standard rTMS[54,55] and theta burst (continuous TBS right and iTBS left)[56] and has recently shown efficacy in older adults.[57,58] Notwithstanding the large effect in the sham group, the lower than expected depression response to active stimulation may reflect an unintended suppression of the antidepressant effects related to the excitatory stimulation of the right DLPFC.

The study has several limitations to be addressed to pursue a definitive randomized-clinical-trial: First, the sample size was very small, increasing the likelihood of false negative results. Second, there was heterogeneity of the EFD of study participants, who likely included

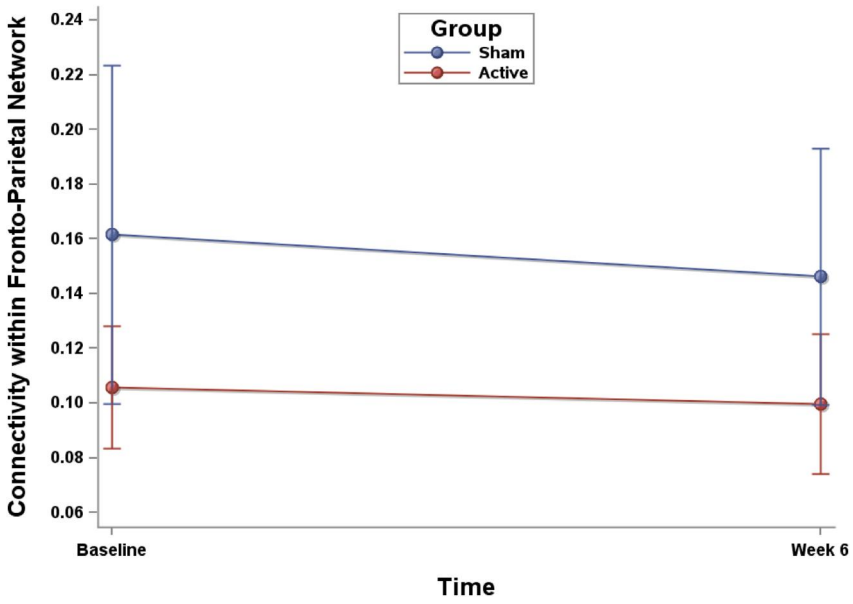

FIGURE 3 Change in connectivity within Fronto-parietal network (FPN) over time

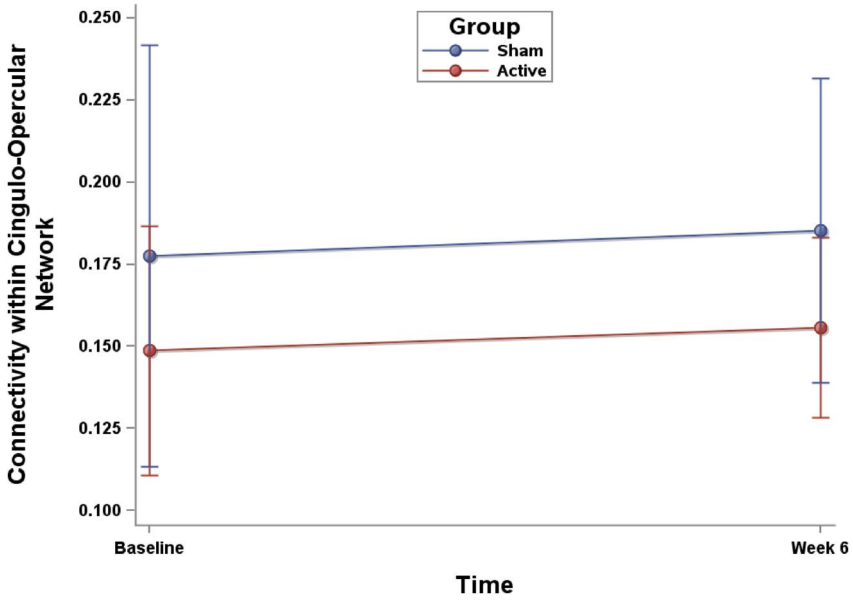

FIGURE 4 Change in connectivity within the Cingulo-opercular network (CON) overtime

those with normal cognitive function as well as those with various degrees of cognitive impairment, as reflected by a wide range of MOCA scores. This heterogeneity highlights the challenges of studying and treating LLD, in that a single diagnostic group may contain subgroups including those with minimal neurodegenerative disease versus those with moderate or even severe neurodegeneration, who may have differential response to treatments such as iTBS. Third, we cannot exclude the possibility that practice effects on the NIH-tool -box executive measures could have limited the ability to detect subtle intervention-related changes in EFD. Fourth, our stimulation target was based on group-level connectivity anticorrelation between the DLPFC and the subgenual cingulate and does not account for individual differences. Given the heterogeneity in EFD, targeting the stimulation based on individualized functional-connectivity maps[59,60] may offer a superior approach to treating LLD with EFD.

In summary, this pilot study showed bilateral iTBS to the DLPFC is feasible and tolerable without serious adverse effects in LLD but preliminary results were unsupportive of the concept of target engagement of the CCN to improve functional disconnectivity putatively underlying LLD. A future RCT to test efficacy and mechanism of this paradigm on depression and EFD requires (a) a larger sample size to include stratification of variables including age, and severity of cognitive, executive impairments and depression severity; (b) refinement in the target-engagement based on individualized functional targets.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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