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EDITORIAL COMMENT
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Can Intermittent Theta-Burst Stimulation of Dorsolateral Prefrontal Cortex Relieve Executive Dysfunction in Patients With Late-Life Depression?

Late-life depression (LLD) is defined as the occurrence of major depressive disorder (MDD) in individuals aged 60 years or older.[1] In contrast to MDD in young populations, LLD is characterized by impairments in various cognitive domains, particularly the executive function deficits (EFD). These deficits encompass the areas of impulse inhibition, cognitive flexibility, planning and organization, and selective attention.[2] Notably, the presence of EFD is indicative of resistance to antidepressant treatment, increased disability, poor quality of life, and an elevated susceptibility to suicide.[3,4] Hence, enhancing the executive function performance of LLD holds considerable clinical importance in improving their prognosis. As the first-line pharmacological interventions, selective serotonin reuptake inhibitors exhibit some efficacy in alleviating depressive symptoms, but their ability to address EFD in LLD patients remains limited.[4] In recent years, psychotherapy has garnered significant attention as a complementary approach to drug therapy. Various forms of psychotherapy, including behavioral activation therapy, cognitive behavioral therapy (CBT), life review therapy, and mindfulness, have been explored.[5] Previous research has demonstrated the potential of CBT in enhancing EFD.[6] Nevertheless, the efficacy of psychotherapy is contingent upon the therapist and treatment process, thereby constraining its broader implementation. Consequently, there is a growing urgency to develop novel treatment techniques that can effectively alleviate EFD in LLD.

From a neuroscientific standpoint, it is posited that disruptions in functional networks may serve as a shared mechanism leading to the manifestation of both persistent depressive symptoms and EFDs. The cognitive control network (CCN),[7] mainly comprising the dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex, postparietal cortex, and frontal eye fields, plays a pivotal role in regulating top-down cognitive processes.[8] Prior research has demonstrated that patients with LLD exhibited decreased resting-state functional magnetic resonance imaging (fMRI) connectivity within the CCN, which was linked to dysexecutive behavior and resistance to antidepressant treatment.[9] Additionally, decreased activity in the DLPFC during cognitive tasks and impaired connectivity between the DLPFC and the dorsal anterior cingulate have been previously observed in individuals with LLD.[10]

Noninvasive brain stimulation, which focuses on specific brain circuits, has emerged as a potential therapeutic approach for LLD with EFD. Intermittent theta-burst stimulation (iTBS), a novel repetitive transcranial magnetic stimulation (rTMS) paradigm, has gained FDA approval for the treatment of depression.[11] This stimulation pattern closely resembles theta rhythms (5-7 Hz), which are known to facilitate long-term potentiation and are associated with learning and memory processes.[12] Our recently conducted meta-analysis has confirmed that iTBS exhibited comparable antidepressant effects and rates of adverse reactions to the traditional 10 Hz rTMS.[13] A noteworthy advantage of iTBS lies in its remarkably brief treatment duration of 3 minutes, in contrast to the 26-minute duration of conventional rTMS.[11] Consequently, iTBS is more beneficial owing to its short sessions, which enable patient treatment with comparable therapeutic effectiveness.

Ilieva et al.[14] revealed a positive correlation between the effects of left-sided TMS targeting the DLPFC and age in terms of cognitive inhibition and cognitive flexibility. Furthermore, investigations employing iTBS in a sample of healthy individuals spanning various age groups suggested that the modulation of executive function varied depending on the task, with older participants exhibiting more pronounced effects.[15] From this perspective, adopting the

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iTBS paradigm may relieve EFD in patients with LLD, but 2 recently published studies seem to have reached opposite conclusions.[16,17]

In the single-arm study published in 2020,[16] a total of 13 patients with LLD and EFD were included, and open-label iTBS was administered bilaterally over the DLPFC for a duration of 4 weeks. The study revealed a noteworthy improvement in the Montgomery–Asberg Depression Rating Scale scores from baseline to treatment end. Additionally, the Flanker inhibitory control and attention test demonstrated a significant enhancement in executive function. Nevertheless, the study's primary limitations encompassed the small sample size and the absence of a sham comparator. Subsequently, a pilot randomized controlled trial (RCT) was undertaken in 2023,[17] wherein 15 older adults diagnosed with depression and EFD were randomly assigned to receive either iTBS or a sham intervention over a period of 6 weeks. The administration of iTBS (or sham) followed a sequential pattern, commencing with the left DLPFC and subsequently targeting the right DLPFC, similar to their prior study.[16] Unfortunately, this pilot study did not provide evidence in favor of the effectiveness of bilateral iTBS as a treatment for depression or EFD in the elderly.

This pilot RCT represents the first attempt to employ bilateral iTBS as a therapeutic intervention for EFD in LLD with a sham group.[17] Despite the limitations associated with a small sample size, there exists a significant factor that could account for the negative results. Prior research has indicated that the sequential bilateral approach involving inhibitory stimulation (1 Hz) to the right DLPFC and excitatory stimulation (10 Hz) to the left DLPFC has exhibited efficacy with standard rTMS[18,19] and continuous theta-burst stimulation (cTBS) on the right and iTBS on the left,[20] and has recently demonstrated effectiveness in older individuals.[21] Thus, excitatory iTBS of the right DLPFC in this pilot RCT may inhibit the antidepressant effect.

In fact, in the large RCT conducted by Blumberger et al,[21] theta-burst stimulation (cTBS right and iTBS left) did not appear to have a beneficial effect on EFD in patients with LLD. A previous meta-analysis demonstrated that cTBS targeting the PFC of healthy groups resulted in a decline in executive function performance.[15] In addition, the authors postulated that iTBS may have a promoting effect on executive processes, especially working memory.[15] Moreover, the study conducted by Cheng et al[22] demonstrated that left prefrontal iTBS, not right prefrontal cTBS, exhibited a positive effect on executive function, which may be unrelated to its antidepressant properties. Consequently, we propose that rigorously designed RCTs should be undertaken to investigate the impact of left iTBS of DLPFC on EFD in individuals with LLD. Furthermore, the current investigations into the mechanism of action of iTBS are still in the early stage. Apart from the CCN that can be observed via neuroimaging, it is also crucial to consider the noteworthy alterations in neurotransmitter levels, such as dopamine and serotonin.

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