Title: Harnessing the Potential of Transcranial Magnetic Stimulation in Geriatric Depression: Emerging Techniques and Findings

Authors Antoine Sader, MD and Rita Khoury, MD

Department of Psychiatry, American University of Beirut, Faculty of Medicine & the Medical Center Beirut, Lebanon

Key highlights:

- Although safe and well-tolerated, conventional transcranial magnetic stimulation (TMS) is found to be less effective in older adults compared to younger populations.
- In treating geriatric depression, Theta burst stimulation (TBS) matches conventional TMS in efficacy and tolerability while offering a much shorter administration time.
- Deep-TMS demonstrates superior efficacy over other TMS methods for geriatric depression, likely due to its deeper and broader brain stimulation.
- Larger, placebo-controlled randomized controlled trials with standardized protocols and extended follow-ups are needed to evaluate and optimize various TMS techniques and protocols for geriatric depression.

Introduction:

By 2050, the global population aged 65 and older is projected to rise from 10% in 2022 to 12%. Alongside this demographic shift, cases of late-life depression are expected to double, presenting a significant public health challenge. Late-life depression currently affects 1.8-7.2% of individuals aged 60 and older, yet it remains frequently underdiagnosed. This is largely due to the overlap with cognitive decline and the atypical presentation of depression symptoms in older adults. Managing geriatric depression is fraught with challenges; alarmingly, up to 81% of patients fail to respond to first-line antidepressants [1]. The situation becomes even more complex with the presence of comorbid medical conditions, polypharmacy, and treatment adherence issues. This underscores the urgent need for alternative therapeutic options for our growing older population.

Electroconvulsive therapy (ECT) remains widely used in geriatric depression, often outperforming pharmacotherapy in older adults. Yet, it is associated with cognitive impairment and rare but serious cardiovascular events. Repetitive transcranial magnetic stimulation (rTMS), an FDA-

approved intervention for depression, emerges as a safer alternative as it uses localized, sub-convulsive electrical stimulation without anesthesia and cognitive side effects [2]. Conventional rTMS for depression targets the dorsolateral prefrontal cortex (DLPFC) with left-sided excitatory or combined left-sided excitatory and right-sided inhibitory stimulation.
Figure 1 shows the different brain regions implicated in geriatric depression, which are potential therapeutic targets for TMS [3]. We summarize below relevant published data on TMS efficacy and safety in the depressed geriatric population.

Efficacy and safety of conventional TMS in geriatric depression

Early studies using outdated TMS parameters yielded mixed results concerning rTMS efficacy for geriatric depression. This inconsistency may stem from variations in study design, antidepressant use, protocol duration, and participant heterogeneity within the older population. As for safety profile, among 11 studies evaluating 353 participants, a systematic review by Overvliet et al. [4] found conventional rTMS safe and well-tolerated in older adults with only 12.4% experiencing mild adverse effects (headache, scalp discomfort) and 1.5% experiencing serious side effect (psychiatric hospitalization, Increased suicidal ideation, seizure, and ophthalmic complication). Predictors of remission in LLD treated with TMS include fewer prior antidepressant treatment failures (one or less), higher session numbers and lower baseline depressive symptom severity. However, most conventional rTMS studies found older age as a predictor of nonresponse. It is postulated that age-related brain atrophy and inadequate rTMS dosing may have contributed to this poor response. Effectively treating geriatric depression with rTMS may require more precise and personalized targeting. This could involve modifying protocols—adjusting intensity, frequency, and pulse duration—or utilizing different devices or coil designs to ensure adequate cortical penetration and enhanced antidepressant effects.

Efficacy and safety of novel TMS techniques in geriatric depression

One exciting new TMS modality is theta burst stimulation (TBS). This technique mimics the brain's natural theta waves linked with synaptic plasticity, by delivering three 50 Hz pulses separated by 200 milliseconds (5 Hz). More importantly, this approach shortens administration time to just 1-2 minutes, compared to 20-40 minutes for conventional rTMS, while maintaining similar efficacy and side effect profiles. Intermittent TBS (iTBS) studied in geriatric depression yielded mixed results, depending on the targeted area and whether the stimulation is excitatory or inhibitory. For instance, one study showed no significant differences in depression scores with bilateral excitatory DLPFC stimulation [5]. Conversely, a non-inferiority randomized controlled trial (RCT) demonstrated that bi-iTBS, with inhibitory frequency on the right DLPFC and excitatory frequency on the left DLPFC, showed positive antidepressive results in treatment-resistant depression in older individuals, comparable to conventional rTMS [6]. Notably, the use of MRI imaging to precisely localize the targeted area likely enhanced the efficacy of iTBS. Surprisingly, right excitatory DLPFC targeting also showed a significant antidepressant effect in depressed older adults challenging the conventional theory of hemispheric asymmetry in emotion regulation. By combining right excitatory iTBS with electric field modeling, Quinn et al. [7] accounted for age-related atrophy and its impact on the induced electric field (|E|) from TMS or

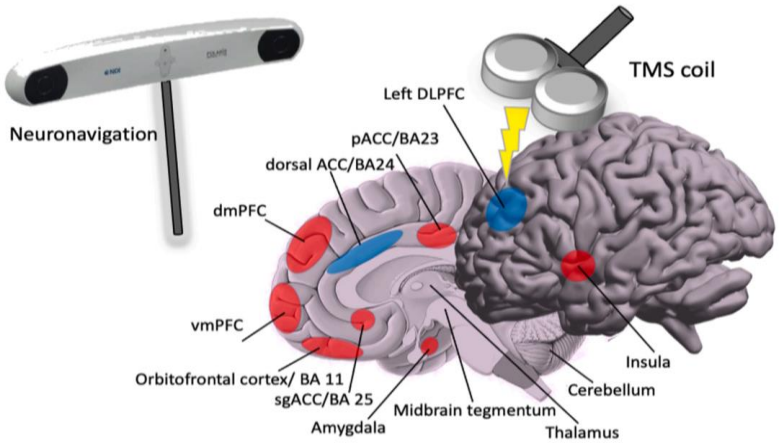
TBS. This precise targeting enables remarkably efficient treatment at safer, lower intensities without sacrificing effectiveness. Even more intriguing, the findings suggest that even if the coil isn't perfectly positioned, a higher |E| with broader distribution can still successfully reach the target, yielding the desired clinical outcomes. This revelation may explain the enhanced benefits of deep-TMS (d-TMS) in geriatric depression, which uses an H-coil to stimulate both hemispheres more deeply and broadly, reaching both the ventrolateral PFC and DLPFC.

Indeed, compared to conventional TMS, iTBS and accelerated iTBS/TMS, d-TMS has shown higher response and remission rates, like those seen in younger populations [8]. This higher effectiveness detected in clinical studies could be attributed to several factors: the higher dose delivered by d-TMS, the larger sample sizes in d-TMS studies, and the deeper, broader brain volume stimulated by d-TMS making it less likely to miss the target and eliminating the need for advanced neuronavigation [8]. Regarding tolerability in older populations, d-TMS is safe and well-tolerated, with only mild and transient adverse effects [8].

Exploring new ways to enhance TMS efficiency for geriatric depression may also involve high-frequency rTMS (HF-rTMS). However, studies have reported higher occurrences of adverse effects with HF-rTMS compared to low-frequency rTMS (LF-rTMS) in the general population. To address these risks while maintaining HF-rTMS's effectiveness, Vidya et al. [9] introduced an innovative two-step approach: pre-treating the right DLPFC with low-intensity HF-rTMS, followed by LF-rTMS. This priming method aims to amplify the neural response while minimizing side effects. The results were compelling, showing significant improvements in response and remission rates for the priming group compared to the sham group, while still having a favorable safety profile. Nonetheless, the study's small sample size limits the generalizability of these findings, and larger RCTs are needed to confirm the results.

Conclusion:

Our review highlights the promising role of TMS as a safe, well-tolerated treatment for geriatric depression. However, its effectiveness can be hindered by age-related brain atrophy and suboptimal targeting and dosing. Among the various TMS protocols, TBS is an interesting and practical modality due to its shorter treatment duration and potential to enhance neuroplasticity. Yet, results from TBS studies have been mixed and heavily influenced by the targeted brain region. D-TMS consistently outperforms other methods, achieving higher response and remission rates. This success is likely due to d-TMS's ability to stimulate deeper and broader brain regions. Furthermore, innovative approaches like high-frequency rTMS and priming protocols are being explored to boost treatment outcomes in the geriatric population. Despite these exciting advancements, there is a pressing need for larger, placebo-controlled RCTs with standardized protocols and extended follow-up periods. Future studies should utilize consistent depression scales and focus on a more representative older population samples, accounting for cognitive status, medical comorbidities, and antidepressant use. Such rigor is essential to accurately compare, refine, and personalize TMS, ultimately identifying optimal protocols for effectively treating geriatric depression.



Brain Networks in Geriatric Depression

Cognitive Control Network (CCN)	DLPFC dorsal ACC	Hypoactivity	Executive Dysfunction
Default Mode Network (DMN)	dmPFC pACC	Hyperactivity	Self-referential thinking, rumination
Salience Network (SN)	Amygdala Insula	Hyperactivity	Apathy, negative thinking, negative bias

Fig 1. Transcranial magnetic stimulation (TMS) and brain networks in geriatric depression. Source: Cappon, D., et al., *Transcranial magnetic stimulation (TMS) for geriatric depression.* Ageing research reviews, 2022. **74**: p. 101531-101531.

Brain regions associated with depressive symptomatology are highlighted (red indicates hyperactivation and blue indicates hypoactivation). Brain networks involved in GD are described in the table alongside their psychological phenotype as well as whether they are hyper- or hypo-activated. DLPFC = dorsolateral prefrontal cortex, pACC = pregenual anterior cingulate cortex, BA = Brodmann area, dmPFC = dorsolateral PFC, vmPFC = ventromedial PFC, sgACC = subgenual anterior cingulate cortex.

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Antoine Sader, MD, holds a medical degree from the University of Balamand and has been a Research Fellow in the Department of Psychiatry at the American University of Beirut since 2023. His primary research interests are neuropsychiatric symptoms associated with neurodegenerative diseases, particularly Alzheimer's and Parkinson's, and novel interventional treatments for Alzheimer's disease. as326@aub.edu.lb

Dr. Rita Khoury is an adult and geriatric Psychiatrist, Assistant Professor of clinical psychiatry at the American University of Beirut, Lebanon**.** rk224@aub.edu.lb