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Review

NEUROMODULATION IN PSYCHOGERIATRICS: EMERGING EVIDENCE AND FUTURE DIRECTIONS

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SUMMARY

Late-life mental illnesses, particularly treatment-resistant late-life depression, present a significant public health challenge due to complex interactions with medical comorbidity, polypharmacy, and neurocognitive disorders. Standard pharmacological treatments are often limited by efficacy and tolerability issues in this population. Neuromodulation has emerged as an essential therapeutic modality, offering targeted treatment that can circumvent systemic side effects. This narrative review provides a critical synthesis of the evidence for established neuromodulation techniques - Electroconvulsive Therapy (ECT), Repetitive Transcranial Magnetic Stimulation (rTMS), Transcranial Direct Current Stimulation (tDCS), and Vagus Nerve Stimulation (VNS) - and explores emerging approaches like Transcranial Focused Ultrasound (tFUS) within psychogeriatric populations. The application of these techniques is governed by a trade-off between efficacy, safety, and logistical burden. ECT remains the gold-standard for severe presentations, such as psychosis or catatonia, despite its cognitive risks. rTMS provides a powerful balance of efficacy and tolerability for non-psychotic TRD. tDCS and non-invasive VNS offer excellent safety profiles and potential for home-based administration, expanding access and showing promise for cognitive indications. While the clinical roles of these modalities are clarifying, the path forward requires addressing critical gaps. Future research must prioritize methodologically rigorous, geriatric-specific trials, the development of biomarkers to guide personalized treatment, and an unwavering focus on the ethical complexities of assessing capacity and obtaining informed consent. Integrating these imperatives will enable the field to deliver precise, effective, and patient-centered care for older adults.

Key words: *neuromodulation - psychogeriatric*

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INTRODUCTION

The aging of the global population has established psychogeriatrics as a public health priority, driven by the rising prevalence of late-life mental illness. Among these conditions, late-life depression is particularly prevalent and disabling (Steffens et al. 2009; S.-C. Wang et al. 2023). As many as half of these patients do not respond to standard antidepressant therapies, leading to treatment-resistant late-life depression (TR-LLD). This condition is associated with significant functional disability, increased medical morbidity, and higher mortality (Defrancesco et al. 2018). The clinical picture is complicated by an interplay with neurocognitive disorders. Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD) can present with overlapping symptoms or exist as a comorbidity, prodrome, or risk factor for TR-LLD, complicating diagnosis and treatment (Mukhopadhyay & Banerjee 2021). Distinguishing the cognitive effects of depression from an underlying neurodegenerative process, is a challenge in for clinicians and a critical distinction for guiding intervention (Fazio et al. 2024). Treatment is often constrained by physiological and medical factors, including high rates of medical comorbidity, pervasive polypharmacy, and age-altered pharmacokinetics, which can increase the risk of adverse events from drugs with a high anticholinergic burden, for instance, frequently limiting the safety and utility of conventional pharmacology (Steffens 2024).

In response to these challenges, neuromodulation has emerged as an essential therapeutic modality in psychogeriatrics. Defined as the alteration of nerve activity through targeted delivery of stimuli to specific neurological sites, its rationale in older adults is compelling. By acting directly on dysfunctional neural circuits, these techniques can circumvent the systemic risks of polypharmacy and may be effective even when pharmacotherapy is compromised by limited efficacy or poor tolerability. Given the high rates of treatment resistance and medication sensitivity in the geriatric cohorts (Gutsmiedl et al. 2020) , neuromodulation is not merely a last resort, but an essential and mechanistically distinct component of the psychogeriatric treatment arsenal.

This narrative review provides a critical synthesis of the evidence for established neuromodulation techniques - namely Electroconvulsive Therapy (ECT), Repetitive Transcranial Magnetic Stimulation (rTMS), Transcranial Direct Current Stimulation (tDCS), and Vagus Nerve Stimulation (VNS) - specifically within psychogeriatric populations. Furthermore, it will explore innovative future directions, with a dedicated focus on Transcranial Focused Ultrasound (tFUS) as a prominent example. Emphasis will be placed on practical applications, comparative considerations relevant to older adults, and key areas for future research in this specialized field.

ELECTROCONVULSIVE THERAPY

ECT is the gold-standard treatment for the most severe presentations of TR-LLD, including cases with psychotic features, catatonia, or high suicide risk (Blumberger et al. 2015; van Rooij et al. 2020; Espinoza & Kellner, 2022; Steffens, 2024). Beyond these primary indications, its utility extends to other difficult-to-treat geriatric conditions, including bipolar depression (Morcos et al. 2021) and, as possibly last line option, for severe behavioral and psychological symptoms of dementia such as agitation and aggression (Williams & Campbell, 2019).

The efficacy of ECT in older adults is particularly robust, with response rates frequently reported between 60% and 80% (Blumberger et al. 2015; Geduldig & Kellner, 2016). Notably, older age itself can be a positive predictor of a rapid response (Huang et al. 2025; O'Connor et al. 2001), with the effectiveness holding even in the "old-old" (e.g., >75 years) (Sarma et al. 2024). While ECT is generally safe even in medically complex older adults, the primary clinical challenge remains the management of cognitive side effects (Espinoza & Kellner, 2022), particularly the higher incidence of post-treatment delirium or confusion in this population (Gardner & O'Connor, 2008). Crucially, advances in ECT technique directly address these risks. The use of right unilateral placement, which causes significantly less severe and persistent retrograde amnesia than bilateral ECT (Gardner & O'Connor, 2008; Sackeim et al. 2007), and ultrabrief pulse width stimulation (Espinoza & Kellner, 2022), are now central to geriatric practice as they significantly improve the cognitive safety profile. Importantly, these cognitive effects are not believed to stem from neural cell damage, a conclusion supported by studies showing a lack of consistent post-ECT changes in peripheral biomarkers of neuronal injury such as S-100b and Neuron-Specific Enolase (Bassa et al. 2021). Although these more modern techniques have reduced some burden, balancing the risks and benefits remain challenging clinical decisions, which are to be made in close collaboration with patients and potential caregivers.

Effective geriatric ECT practice therefore begins with a meticulous pre-treatment workup, including a careful anesthetic and cardiovascular risk assessment (Espinoza & Kellner, 2022) and a baseline cognitive screen to monitor for any changes (Gardner & O'Connor, 2008). Another consideration is the long-term management of this recurrently ill population. Continuation or maintenance ECT has proven to be an indispensable strategy for relapse prevention (Geduldig & Kellner, 2016; van Schaik et al. 2012). Continuation or maintenance ECT is well-tolerated, and its efficacy in preventing relapse is comparable to continuation pharmacotherapy, making it a vital option for sustaining wellness by reducing rehospitalizations (van Schaik et al. 2012). For instance, one randomized trial in older adults demonstrated a significantly lower relapse rate at one year for patients receiving maintenance ECT compared to placebo (37% vs. 84%) (van Schaik et al. 2012), while another study found that continuation ECT combined with medication led to lower relapse rates and longer time to relapse than medication alone (Gagné et al. 2000).

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS)

As a less invasive alternative to ECT, rTMS is an established neuromodulation technique that uses focused magnetic pulses to induce electrical currents, thereby modulating the excitability of targeted cortical regions implicated in mood regulation (Gálvez et al. 2015; Miron et al. 2021). In older adults, the majority of research has looked at rTMS for late-life depressive disorder, particularly treatment-resistant depression (Thakurdesai et al. 2017; S.-C. Wang et al. 2023). Beyond depression, rTMS is also being investigated for emerging applications in psychogeriatrics, including the amelioration of refractory auditory hallucinations, mild and severe neurocognitive impairment (Martins et al. 2017; Thakurdesai et al. 2017).

The evidence base supporting the efficacy of rTMS in TR-LLD has grown substantially, with meta-analytic data now confirming its superiority over control conditions in achieving both response and remission (Valiengo et al. 2022; Zhang et al. 2023). While some earlier studies suggested an inverse relationship between age and efficacy, often linked to factors like frontal atrophy (Cappon et al. 2022), more recent and larger-scale data demonstrate that older adults (≥60 years) achieve response and remission rates comparable to, or in some cases significantly better than, younger adults (Harika-Germaneau et al. 2025; Leuchter et al. 2024; Slan et al. 2024). The evolution of protocols has further enhanced its applicability; notably, theta-burst stimulation (TBS) has demonstrated non-inferiority to standard, longer rTMS protocols for TRD in older adults, with the crucial advantage of achieving this comparable efficacy in significantly shorter session times (Blumberger et al. 2022; Lan et al. 2023; Tao et al. 2025).

A significant clinical advantage of rTMS, particularly in the often multimorbid and medication-sensitive geriatric population, is its highly favorable safety profile (McDonald, 2016; van Rooij et al. 2020). The most common adverse events are mild and transient, typically consisting of headache and scalp discomfort at the stimulation site (Overvliet et al. 2021). The risk of inducing a seizure is very low and comparable to that in younger populations (Overvliet et al. 2021). Critically for the geriatric population, rTMS is not associated with significant adverse cognitive effects; on the contrary, multiple studies have demonstrated its cognitive safety, with some even suggesting potential for cognitive improvement as depressive symptoms lift (Blumberger et al. 2022; van Rooij et al. 2020).

This body of evidence translates into several key clinical pearls for the application of rTMS in older adults. It is a suitable option for those with TRD who cannot tolerate or prefer to avoid pharmacotherapy or ECT (Steffens, 2024). However, successful treatment may necessitate parameter adjustments to account for age-related brain changes, such as using higher stimulation intensity to compensate for cortical atrophy (Cappon et al. 2022; Gálvez et al. 2015). Neuronavigation can also be used to enhance targeting precision (Harika-Germaneau et al. 2025). While the dramatically shorter session times of TBS substantially reduce the treatment burden for patients and caregivers, clinicians should be aware that it may be associated with slightly higher transient pain scores at the stimulation site compared to standard rTMS protocols.

TRANSCRANIAL DIRECT CURRENT STIMULATION

Transcranial direct current stimulation (tDCS) is a non-invasive technique that uses weak, direct electrical currents delivered via scalp electrodes to modulate cortical excitability and brain activity (McDonald, 2016; van Rooij et al. 2020). Its investigated indications in geriatrics include mental health conditions such as depression and cognitive enhancement (McDonald, 2016; Rangarajan et al. 2021), and non-psychiatric explorations including pain management (Martorella et al. 2023) and even balance impairment to mitigate fall risk(Bueno et al. 2024). Its efficacy in older adults is often variable, and it is typically viewed as an adjunctive or augmentation strategy (Rangarajan et al. 2021; van Rooij et al. 2020). This variability underscores the modality's primary challenge: the need to define optimal parameters and identify patient subgroups who stand to benefit most, though its potential is clearly enhanced when combined with concurrent neuromodulation, pharmacological, and non-pharmacological interventions like cognitive training (Martins et al. 2017; McDonald, 2016).

The compelling rationale for the growing interest in tDCS for older adults is its exceptional safety profile and minimal side effect burden (Martins et al. 2017; Rangarajan et al. 2021). Adverse events are typically mild and transient, consisting of localized itching, tingling, or headache at the electrode site (Martins et al. 2017; Rangarajan et al. 2021). This high degree of tolerability, coupled with its portability and low cost, makes tDCS a uniquely strong candidate for domiciliary (home-based) application - a model that could dramatically improve treatment access for frail or geographically isolated older adults(Rangarajan et al. 2021). The clinical viability of this home-based model was robustly demonstrated in a pivotal pilot RCT, which confirmed that caregiver-administered tDCS was feasible, acceptable, safe, and potentially efficacious for pain management in the challenging population of older adults with AD and related dementias (Martorella et al. 2023).

To translate these promising pilot findings into widespread clinical practice, future research must focus on establishing standardized protocols that address key implementation variables (Martorella et al. 2023; Rangarajan et al. 2021). A first priority is defining optimal patient selection criteria, including methods to assess the capacity and willingness of patients, (and caregivers in at-home models) who are essential for procedural success (Rangarajan et al. 2021). Concurrently, developing user-friendly device interfaces and effective remote monitoring systems is crucial for ensuring treatment fidelity and safety outside the clinical setting (Rangarajan et al. 2021). Ultimately, the broader clinical utility of tDCS in psychogeriatrics is dependent on larger-scale trials to confirm efficacy and refine the specific operational guidelines required for its safe deployment (Martorella et al. 2023).

VAGUS NERVE STIMULATION (VNS)

Vagus nerve stimulation (VNS) modulates brain function via stimulation of afferent vagal fibers that project to brainstem nuclei like the nucleus tractus solitarius, which in turn influences widespread brain networks, including the locus coeruleus-norepinephrine system (Vonck et al. 2014). In clinical practice, VNS presents as two distinct modalities with vastly different risk-benefit profiles for the older adult: the established, surgically implanted device and its emerging non-invasive counterpart.

Implantable VNS

The established role for implantable VNS is as a long-term adjunctive treatment for the most intractable cases of chronic or recurrent treatment-resistant depression (TRD) (van Rooij et al. 2020; Vonck et al. 2014). However, its application in older, often multimorbid individuals requires careful clinical calculus. Candidacy must be weighed against the considerable burdens of surgical implantation and long-term device management, including the eventual need for re-operation for battery replacement (Longpré-Poirier et al. 2024). This long-term aspect introduces unique clinical considerations, such as recognizing impending battery failure through subtle changes in side effects like stimulation pain, which can precede official device warnings (Longpré-Poirier et al. 2024).. While foundational data from epilepsy trials established its general feasibility and safety in adults over 50 (Sirven et al. 2000), its role in psychogeriatrics remains reserved for the most severe and highly refractory cases.

Non-invasive Transcutaneous VNS (tVNS)

In stark contrast to the invasiveness of its predecessor, non-invasive transcutaneous VNS (tVNS) is emerging as a compelling alternative for older adults, offering a potentially much better tolerability profile by avoiding surgical risks entirely (Naparstek et al. 2023; Trifilio et al. 2023, 2023; van Rooij et al. 2020). While its evidence base is still developing, tVNS is opening a new therapeutic avenue for psychogeriatric conditions beyond depression, particularly for cognitive impairment (van Rooij et al. 2020). This potential was substantiated in a large, landmark RCT demonstrating that transcutaneous auricular VNS (taVNS) led to significant improvements across multiple cognitive domains in patients with MCI, establishing both its efficacy and safety in this key psychogeriatric population (Wang et al. 2022).

Ultimately, the clinical choice between VNS modalities in psychogeriatrics is a study in contrasts. Implantable VNS is a higher burden, high-risk option, reserved for a small subset of older adults with the most intractable forms of depression where its significant demands may be justified. Typically patients will have responded to other neuromodulation strategies, such as rTMS and ECT, but in whom maintenance treatment is complicated or associated with severe side-effects. Conversely, tVNS represents a low-risk, less burdensome, and promising therapeutic path, particularly for cognitive indications like MCI, but remains understudied and inaccessible to many (Naparstek et al. 2023; Trifilio et al. 2023).

INTEGRATED COMPARATIVE ASPECTS AND CLINICAL CHOICE

The decision to employ a specific neuromodulation technique in an older patient represents a clinical decision which balances the trade-offs between efficacy, tolerability, and logistical burden. The choice is fundamentally guided by the clinical scenario, from illness severity and specific symptom targets to the patient's underlying frailty and cognitive status (van Rooij et al. 2020). For the most severe presentations - including depression with psychotic features, profound suicidality, or catatonia - ECT remains the first line, most effective and often life-saving intervention (Steffens, 2024; S.-C. Wang et al. 2023). In contrast, while also indicated for treatment-resistant depression, repetitive transcranial magnetic stimulation (rTMS) is less effective for psychotic or catatonic states but presents a powerful option for non-psychotic depression (van Rooij et al. 2020). The risk-benefit calculus differs starkly between modalities. ECT carries significant, albeit manageable, cardiovascular risks and a well-documented potential for cognitive side effects that require careful mitigation strategies (Geduldig & Kellner, 2016; van Rooij et al. 2020). This contrasts with the more benign side-effect profile of rTMS, where adverse events are typically limited to transient headache or focal discomfort, and the exceptionally high safety profile of transcranial direct current stimulation (tDCS), whose minimal side effects make it particularly suitable for frail individuals. At the highest-burden end of the spectrum, implantable VNS necessitates weighing therapeutic goals against surgical risks and the tolerability of chronic side effects like. Finally, logistical and accessibility considerations are critical. The high burden of clinic-based ECT or rTMS can be a barrier, although the development of much shorter theta-burst stimulation (TBS) protocols for rTMS has dramatically reduced treatment time, improving its feasibility (Miron et al. 2021). The unique potential for caregiver-administered, home-based tDCS represents a paradigm shift in accessibility, surmounting the mobility and transportation challenges often faced by older adults. Ultimately, the optimal therapeutic path is a personalized one, integrating these clinical factors with baseline cognitive function and, most importantly, the values and preferences of the patient and their carers (Shlobin & Rosenow, 2022; van Schaik et al. 2012)

EMERGING EVIDENCE AND FUTURE DIRECTIONS

Transcranial focused ultrasound (tFUS) is an emerging non-invasive modality that utilizes focused acoustic energy to achieve therapeutic effects in specific brain regions. Related terms for its non-ablative application include Low-Intensity Focused Ultrasound (LIFU) and Transcranial Pulse Stimulation (TPS) (Jeong et al. 2025; Zhong et al. 2023). Its non-invasive nature is a key advantage, contributing to a positive perception among the general public when compared to more invasive methods (Atkinson-Clement et al. 2025). In psychogeriatrics, its application is being most actively explored for neurodegenerative disorders.

tFUS operates through several distinct biological mechanisms. First, it can achieve direct neuromadulation by altering neural circuit activity, as demonstrated by enhanced functional connectivity following stimulation of the dorsolateral prefrontal cortex (Jeong et al. 2025). Second, it can exert non-thermal mechanical effects, such as the fragmentation of pathological protein aggregates (Nicodemus et al. 2019). Third, and perhaps most novelly, tFUS can be used to transiently and safely open the blood-brain barrier (BBB), creating a gateway for the targeted delivery of therapeutic agents (Patwardhan et al. 2024; Rezai et al. 2020).

The primary emerging application for tFUS in psychogeriatrics has been in AD and other dementias, where early human trials have shown its potential for cognitive enhancement and modifying underlying pathology (Jeong et al. 2025; Patwardhan et al. 2024). While its application has been extended to Parkinson's disease with studies assessing motor improvement (Nicodemus et al. 2019), its role in primary mood disorders remains largely unexplored in comparison, representing a significant gap in the current research landscape. The precision of these applications is critically enhanced by image-guidance systems, such as MRI-guided tFUS or fMRI-based neuronavigation, which allow for the precise anatomical targeting essential for modulating specific brain circuits (Jeong et al. 2025; Nicodemus et al. 2019; Patwardhan et al. 2024).

While the non-invasive nature of tFUS is a clear advantage, specific safety considerations for older adults, such as the influence of age-related changes in skull density and vascular health, require further investigation (Lee et al. 2021). The main safety concern identified in early AD trials was related to cerebral microhemorrhages, indicating that patients with significant cerebrovascular disease require careful screening (Patwardhan et al. 2024). To date, efficacy data in geriatric samples are encouraging but preliminary, suggesting tFUS is feasible and well-tolerated in older adults with AD and may produce modest improvements in cognition and beneficial biological effects, such as increased regional cerebral perfusion (Jeong et al. 2025; Nicodemus et al. 2019; Patwardhan et al. 2024). Thus, the current evidence positions tFUS as a highly promising but nascent modality in psychogeriatrics, with its most substantive, albeit preliminary, human data centered on the challenges of AD.

CONCLUSION

The evidence reviewed demonstrates that neuromodulation has evolved from a treatment of last resort into a structured and integral component of the psychogeriatric therapeutic algorithm, offering distinct modalities for specific clinical scenarios. The application of these techniques is governed by a sophisticated trade-off between therapeutic efficacy, safety, and logistical burden. ECT remains the established benchmark for high-acuity situations where achieving a rapid and robust response for conditions like psychosis or catatonia is the paramount clinical objective. rTMS occupies a critical middle ground, providing a balance of substantial efficacy for treatment-resistant depression with a more favorable side-effect profile than ECT. Finally, the value proposition for techniques like tDCS and non-invasive VNS lies primarily in their high degree of tolerability and their potential to address logistical barriers to care through home-based administration, making them suitable for different patient subgroups or as adjunctive interventions. The existence of this diverse therapeutic spectrum underscores the necessity of a highly personalized and evidence-based approach to treatment selection.

This review simultaneously highlights critical gaps in the evidence base that currently limit the field's potential and must be addressed for its maturation. The path forward is defined by several essential imperatives. The first is methodological: it is imperative to establish a dedicated geriatric-specific evidence base through rigorous trials that can properly account for the influence of age-related neurobiology, medical comorbidity, and polypharmacy on treatment outcomes. Second is the personalization imperative, a central goal to move beyond broad patient selection criteria and toward biomarker-guided treatment to more reliably predict response and optimize outcomes. Finally, all technological and clinical progress must be paralleled by an unwavering focus on the ethical imperative, ensuring robust and sensitive processes for determining capacity and securing valid informed consent in a potentially vulnerable population. It is this integration that will enable the field to fully deliver on its promise of providing precise, effective, and patient-centered care.

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Laurent Elkrief is a founder at OneCare Biotechnologies, a mental health biotechnologies startup. His work at OneCare is not in any way related to the present work.

Contribution of individual authors:

Both Authors contributed to the literature search and the drafting of the text.

Both authors approved the final manuscript.

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