Neuromodulation of Memory Function in Aging: Mechanisms, Evidence, and Clinical Prospects

Shrey Grover [1], Robert M. G. Reinhart [1-5]

[1] Department of Psychological and Brain Sciences, Boston University, Boston, MA, USA
[2] Department of Biomedical Engineering, Boston University, Boston, MA, USA
[3] Center for Systems Neuroscience, Boston University, Boston, MA, USA
[4] Cognitive Neuroimaging Center, Boston University, Boston, MA, USA
[5] Center for Research in Sensory Communication and Emerging Neural Technology, Boston University, Boston, MA, USA.

Correspondence to:
Robert M. G. Reinhart
111 Cummington Mall, Rm 264
Boston, MA 02215
Email: rmgr@bu.edu

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Abstract

Declining memory function is one of the most prevalent and consequential cognitive changes associated with aging, with profound implications for quality of life. These deficits are further exacerbated in pathological conditions such as mild cognitive impairment (MCI) and Alzheimer's disease (AD). Although pharmacological interventions continue to be explored, their limited efficacy has underscored the need for alternative approaches. Neuromodulation has emerged as a promising strategy for directly targeting the neural circuits that support memory. A growing body of research, spanning invasive and noninvasive techniques, multiple cortical and subcortical targets, and diverse mechanisms of action, suggest that modulating neural activity can meaningfully influence memory function. In this review, we synthesize current advances in the application of neuromodulation to age-related memory decline in healthy older adults, as well as in individuals with MCI and AD. We first outline the neural mechanisms underlying memory impairment that are amenable to modulation, followed by an overview of major neuromodulation approaches and their operating principles. We then evaluate evidence from both invasive and noninvasive interventions aimed at enhancing memory. Finally, we discuss key methodological challenges and future directions, highlighting the potential of neuromodulation to support cognitive rehabilitation and promote adaptive plasticity in memory networks.

1. Introduction: Memory Decline and the Need for Circuit-Based Interventions

Age-related decline in memory function is among the most common and disabling cognitive changes associated with aging [1–4]. As global populations age, impairments in memory are increasingly recognized as a major public health challenge, affecting independence, quality of life, and the ability of older adults to engage fully in daily activities [5]. Memory dysfunction also represents one of the earliest and most prominent features of neurodegenerative disease, particularly Alzheimer's disease [6]. Consequently, identifying interventions that can preserve or restore memory function in older adults has become a central goal of both cognitive neuroscience and neurorehabilitation [7–9].

Memory decline in aging exists along a continuum. At one end are changes associated with healthy cognitive aging, which commonly include slower encoding of new information [10], reduced associative memory [11,12], and increased susceptibility to interference [13]. Many older adults experience these changes without meeting criteria for clinical impairment [14], yet the functional consequences can still be meaningful in everyday life [15]. A second stage involves mild cognitive impairment (MCI), a condition characterized by measurable cognitive decline that exceeds what would be expected for age while largely preserving independence in daily activities [16]. MCI, particularly when memory is prominently affected, is often considered a prodromal stage of Alzheimer's disease [17]. At the far end of the continuum lies Alzheimer's disease and related dementias, in which progressive degeneration of memory circuits leads to severe impairments in episodic memory, learning, and other cognitive domains [18].

Traditional therapeutic strategies for memory impairment in aging have relied primarily on pharmacological approaches targeting neurotransmitter systems [19], such as cholinergic [20] or glutamatergic signaling [21]. While these medications can provide modest symptomatic benefits for some patients, their effects are generally limited and do not halt the underlying progression of cognitive decline [22,23], and can cause significant side effects [24]. Moreover, pharmacological interventions act broadly across the brain and, in principle, can cause paradoxical effects whereby they improve some target cognitive functions while impairing other non-target functions [25]. These limitations have motivated growing interest in alternative approaches that directly engage and modulate the neural systems responsible for cognitive processing [26,27].

In recent years, neuromodulation has emerged as a promising strategy for influencing brain function at the level of neural circuits and networks [28]. Neuromodulation refers broadly to a set of techniques that alter neural activity through electrical, magnetic, acoustic, or other forms of stimulation [29,30]. Some approaches, such as deep brain stimulation, involve implanted devices that deliver stimulation directly to specific brain regions [31]. Others are noninvasive methods, including transcranial electrical stimulation, transcranial magnetic stimulation, focused ultrasound, and vagus nerve stimulation, which can influence brain activity without surgery [29,30]. These technologies have been widely explored in movement disorders and psychiatric conditions [32–35], and more recently they have begun to attract increasing attention as potential tools for cognitive rehabilitation [36–41].

One of the key motivations for applying neuromodulation to memory decline is the growing understanding that memory depends on coordinated activity across distributed brain networks [42–46]. Memory processes rely on dynamic interactions among the hippocampus, prefrontal cortex, parietal cortex, and other regions that communicate through rhythmic patterns of neural activity (**Fig. 1A**) [42,45,47–52]. Aging and neurodegenerative disease disrupt these network interactions, altering the timing and synchronization of neural signals that support encoding, consolidation, and retrieval of memories (**Fig. 1B**) [41,53]. Neuromodulation technologies offer the possibility of restoring or enhancing these network dynamics by directly influencing the physiological mechanisms that coordinate neural communication [41].

From a neurorehabilitation perspective, neuromodulation is particularly appealing because it can potentially be combined with behavioral interventions, cognitive training, and other therapeutic strategies to promote adaptive plasticity in memory circuits [54–57]. Rather than acting solely as a symptomatic treatment, neuromodulation may help create neural conditions that facilitate learning and recovery. As a result, stimulation-based approaches are increasingly being investigated not only as standalone interventions but also as tools that can augment cognitive rehabilitation programs [58,59].

The goal of this chapter is to review current advances in neuromodulation approaches aimed at improving memory function in older adults. We begin by examining the neural mechanisms that contribute to memory decline in aging and why these mechanisms represent promising targets for neuromodulation. We then discuss the principles by which stimulation technologies can influence neural circuits, followed by a review of both noninvasive and invasive neuromodulation methods that have been investigated for memory enhancement. Finally, we summarize evidence from clinical studies, consider current limitations and challenges, and discuss emerging directions that may shape the future of neuromodulation in cognitive neurorehabilitation.

2. Neural Mechanisms of Memory Decline in Aging

Age-related changes in memory arise from a combination of structural, functional, and physiological alterations across distributed brain networks that support learning and memory [60–64]. Although the hippocampus plays a central role in episodic memory formation, memory processes depend on coordinated activity among multiple cortical and subcortical regions, including the prefrontal cortex, parietal cortex, and medial temporal lobe structures (**Fig. 1A**) [42–46]. Aging affects many components of these systems, leading to changes in how information is encoded, stored, and retrieved. Understanding these mechanisms is important not only for explaining cognitive decline but also for identifying physiological targets for neuromodulation-based interventions.

2.1 Memory systems most affected in aging

Not all memory systems are equally vulnerable to aging [1]. Among the most consistently affected domains is episodic memory, which refers to the ability to remember personally experienced events and the contextual details associated with them [65]. Older adults

often show reduced accuracy in recalling memories [66,67] and may have difficulty binding together the elements of an event, such as objects, locations, and temporal context [68,69]. These deficits are thought to reflect impairments in hippocampal-dependent encoding and retrieval processes [70,71].

Another commonly affected domain is associative memory, which involves linking together multiple pieces of information [72]. For example, remembering the face associated with a person's name or the location of an object in a room requires forming associations between distinct representations. Older adults frequently show particular difficulty with these types of tasks [11,12,73], even when memory for individual items remains relatively preserved [74]. This pattern suggests that aging disproportionately affects the mechanisms that integrate distributed neural representations into coherent memories.

Working memory, the ability to temporarily maintain and manipulate information, can also show age-related decline [75,76], particularly when tasks require maintaining multiple items [77] or resolving interference from competing information [78]. Although working memory relies heavily on prefrontal cortical networks rather than the hippocampus alone [79], interactions between prefrontal and medial temporal regions are often required for complex memory operations [45]. Changes in these network interactions may therefore contribute to age-related deficits across multiple memory domains [80].

2.2 Circuit-level changes in aging

At the neural level, aging is associated with alterations in the structure and function of brain circuits that support memory [81–83]. One of the most well-documented changes involves the hippocampal-prefrontal network, which plays a critical role in encoding and retrieving episodic memories. Structural imaging studies have shown age-related reductions in hippocampal volume [81,83,84], particularly in subfields such as CA1 and the dentate gyrus [85]. Functional imaging studies further indicate that communication between the hippocampus and prefrontal cortex becomes less efficient with age [86–89], potentially impairing the coordination of memory processes.

Another hallmark of aging is a reduction in network specificity, sometimes described as neural dedifferentiation [90]. In younger adults, cognitive tasks typically recruit relatively specialized neural populations that represent specific types of information. In older adults, neural responses often become less selective, with broader and more overlapping patterns of activation across cortical regions [91–93]. This reduced specificity may reflect declines in inhibitory processes or alterations in synaptic connectivity, leading to less precise neural representations [90,94,95].

At the same time, the aging brain often shows evidence of compensatory recruitment, in which additional brain regions are engaged to support cognitive performance [96–99]. For example, older adults frequently exhibit increased bilateral prefrontal activation during memory tasks compared with younger individuals [98,100,101]. Such recruitment may reflect attempts by the brain to maintain performance despite declining efficiency in primary memory circuits [96–99]. The degree to which an individual is able to successfully engage

such compensatory mechanisms may contribute to their cognitive success, and may be part of the reason for the variability in cognition across older people.

2.3 Oscillatory mechanisms supporting memory

In addition to structural and functional changes in large-scale networks, aging also affects the temporal dynamics of neural activity that coordinate communication between brain regions [53,102–107]. Neural oscillations (i.e., rhythmic fluctuations in neuronal excitability) are thought to play a key role in organizing information processing across distributed circuits [47,49]. Several oscillatory patterns have been implicated in memory function, including theta (approximately 4-8 Hz), gamma (approximately 30-100 Hz), and alpha (approximately 8-12 Hz) rhythms [48,52,108–112].

One of the most extensively studied mechanisms is theta-gamma coupling, in which faster gamma activity is nested within the phase of slower theta oscillations [113,114]. This interaction is believed to support the encoding of sequential information and the binding of multiple memory elements [111]. Evidence from electrophysiological recordings in both animals and humans suggests that coordinated theta and gamma activity within hippocampal-cortical circuits plays an important role in episodic memory formation and during working memory maintenance [51,115–120].

Aging appears to disrupt several aspects of these oscillatory dynamics. Older adults often show reduced theta power during memory encoding and retrieval [121–123], as well as altered coupling between theta and gamma rhythms [106,107,124]. These changes may impair the precise temporal coordination needed for effective communication between the hippocampus and neocortical regions [107]. Additionally, alterations in alpha oscillations, often associated with attentional control and inhibitory processes, may contribute to difficulties filtering irrelevant information during memory tasks [125,126].

2.4 Why these mechanisms are promising targets for neuromodulation

The physiological mechanisms described above highlight several features of memory circuits that make them attractive targets for neuromodulation. First, since many aspects of memory function depend on coordinated rhythmic activity across distributed networks [53,104–107], interventions capable of influencing neural oscillations could potentially restore more effective communication among memory-related brain regions [40,107].

Second, the circuits involved in memory are highly plastic, meaning that their functional properties can be modified through experience and training [127–129]. Neuromodulation techniques that influence synaptic plasticity or network excitability may therefore help promote adaptive changes in memory circuits when paired with behavioral interventions or cognitive training [35,54,59,130].

Finally, the network disruptions observed in aging often involve changes in timing and synchronization rather than complete loss of neural structure [53]. This distinction is important because it implies that some cognitive deficits may arise from dysregulated neural dynamics that remain amenable to modulation. By influencing oscillatory activity,

excitability, or neuromodulatory signaling, stimulation-based approaches may help restore more efficient patterns of communication within memory networks [40,41,131].

These considerations provide a physiological rationale for exploring neuromodulation as a potential strategy for improving memory function in older adults. The following section therefore examines the principles by which stimulation technologies can influence neural circuits and how these mechanisms may be leveraged to support cognitive rehabilitation.

3. Principles of Neuromodulation for Memory Enhancement

Neuromodulation technologies aim to influence brain function by altering the activity of neural circuits that support cognition and behavior. Although the specific mechanisms vary across stimulation modalities, many approaches share a common objective: to modify patterns of neural activity in ways that promote more effective communication within distributed brain networks. In the context of memory enhancement, neuromodulation is typically designed to influence the excitability, timing, or plasticity of neural systems that support encoding, consolidation, and retrieval processes. Understanding the principles by which neuromodulation affects neural circuits is important for interpreting experimental findings and for designing clinically effective stimulation protocols. Several conceptual frameworks have emerged to explain how stimulation may influence cognitive function, including modulation of neuronal excitability, entrainment of neural oscillations, and facilitation of synaptic plasticity [40,131]. These mechanisms are not mutually exclusive and may interact depending on the stimulation method, stimulation parameters, and the physiological state of the brain at the time of stimulation [40,131].

3.1 Conceptual framework: modulation versus stimulation

The term *brain stimulation* can be misleading if interpreted as simply activating neural tissue. In most cases, particularly when performed noninvasively, the goal of neuromodulation is not to directly drive neural firing but rather to shift the probability that neurons will respond to ongoing inputs [132,133]. In this sense, many neuromodulation techniques act more as modulators of neural dynamics than as direct sources of neural activation.

For example, transcranial electrical stimulation typically produces electric fields that are too weak to trigger action potentials directly [134]. Instead, these fields can subtly alter the membrane potential of neurons, slightly increasing or decreasing their excitability [132,133]. This shift can bias how neurons respond to synaptic input, thereby influencing the activity of larger networks. Similarly, certain magnetic techniques such as theta-burst stimulation may modify the responsiveness of neural populations rather than imposing entirely new activity patterns [135].

From a cognitive perspective, this distinction is important because memory processes depend on ongoing interactions within complex neural systems. Rather than replacing these processes, neuromodulation seeks to shape the neural conditions under which

memory-related computations occur, potentially enhancing the efficiency or stability of those processes.

3.2 Key mechanisms of action

Several mechanisms have been proposed to explain how neuromodulation influences memory-related neural circuits (**Fig. 1B**). One mechanism is inducing a change in the overall excitability of a target region or network of interest [136], which is susceptible to age-related changes. For instance, aging involves shifts in overall excitability patterns of the cortex [100] which can be temporarily reversed using stimulation methods designed to manipulate cortical excitability [137].

Another widely discussed mechanism is neural entrainment, in which external stimulation interacts with endogenous neural oscillations [138]. Many cognitive functions depend on rhythmic activity that coordinates communication between brain regions. When stimulation is delivered at frequencies that correspond to intrinsic oscillatory rhythms, it may synchronize neural populations or stabilize oscillatory patterns that support information processing [139]. For example, stimulation in the theta frequency range has been investigated as a means of influencing hippocampal-cortical interactions involved in memory encoding [140].

A third mechanism involves synaptic plasticity, the activity-dependent strengthening or weakening of synaptic connections, driven by changes in the relative timing or pre- and post-synaptic activity. This mechanism has been confirmed in certain forms of stimulation [141–143], while supportive evidence in other forms of stimulation continues to accumulate [144–147]. Repeated stimulation protocols may therefore produce lasting changes in neural circuits that extend beyond the period of stimulation itself [148–153]. Such plastic changes are particularly relevant for neurorehabilitation, where the goal is often to support long-term improvements in cognitive function.

Neuromodulation may also influence network synchronization, which refers to the coordinated timing of activity across distributed neural populations [107,154–156]. Memory processes require precise temporal coordination between the hippocampus and multiple cortical regions. Disruptions in this coordination can impair the integration of information across brain systems. By modifying the timing relationships among neural signals, stimulation may help restore more effective communication within these networks [107].

In addition to influencing local neural activity and network dynamics, some neuromodulation approaches act through ascending neuromodulatory systems that regulate brain-wide states related to attention, arousal, and learning [157] . Neurotransmitter systems such as the cholinergic, noradrenergic, and dopaminergic systems play important roles in modulating memory processes by influencing synaptic plasticity and neural excitability across distributed circuits. These neuromodulatory systems provide an additional pathway through which stimulation-based interventions may influence memory function. Rather than directly targeting a single cortical region, some interventions may operate by engaging broader neuromodulatory networks that regulate plasticity across multiple brain systems.

Finally, the effects of neuromodulation are often state dependent [158,159]. The impact of stimulation can vary depending on the ongoing activity of the brain [160], the cognitive task being performed [161], and the broader physiological state of the individual [162]. For example, stimulation applied during memory encoding may have different effects than stimulation applied during consolidation or retrieval [163]. Similarly, stimulation paired with cognitive training tasks may produce stronger effects than stimulation delivered at rest [164]. Recognizing these state-dependent effects has become increasingly important in the design of modern neuromodulation protocols [159].

3.3 Timing and targeting of stimulation

The effectiveness of neuromodulation depends critically on how stimulation is targeted in both space and time. Spatial targeting refers to the brain regions or networks that are influenced by stimulation. Some approaches focus on modulating activity in cortical regions that are strongly connected to deeper memory structures such as the hippocampus [165,166]. Other methods attempt to influence distributed networks by stimulating multiple regions or by exploiting connectivity patterns within large-scale brain systems [107,155].

Temporal targeting refers to the alignment of stimulation with neural rhythms or behavioral events. Because many memory-related processes unfold on specific timescales, the timing of stimulation relative to neural activity can be an important determinant of its effects. For example, stimulation delivered at specific phases of ongoing oscillations may enhance communication between brain regions or facilitate synaptic plasticity [167,168]. Similarly, stimulation delivered during periods of heightened neural plasticity, such as during learning tasks, may produce larger or more durable effects [169].

Together, these principles provide a framework for understanding how neuromodulation technologies may influence memory-related brain circuits. The following sections review specific stimulation approaches that have been investigated for enhancing memory function in older adults, beginning with noninvasive brain stimulation techniques.

4. Noninvasive Brain Stimulation Approaches

Noninvasive neuromodulation techniques have received increasing attention as potential tools for enhancing memory function in aging populations [170] (**Fig. 2**). These approaches can influence neural circuits without the need for surgical implantation, making them attractive candidates for clinical translation and integration into neurorehabilitation programs. Several stimulation modalities have been investigated, each differing in the physical principles used to influence neural activity and in the types of neural mechanisms they are thought to engage.

In general, noninvasive stimulation approaches aim to modulate cortical excitability, influence oscillatory dynamics, or engage neuromodulatory systems that support plasticity in memory circuits. Because many memory processes depend on coordinated

activity across distributed networks, including the hippocampus, prefrontal cortex, and parietal cortex, stimulation is often applied to cortical regions that are strongly connected to deeper medial temporal lobe structures (**Fig. 1A**). In this way, noninvasive stimulation may indirectly influence hippocampal-cortical interactions that support memory formation and retrieval.

4.1 Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is among the most widely studied noninvasive neuromodulation techniques for cognitive enhancement [171]. In tDCS, a weak constant electrical current is delivered between electrodes placed on the scalp [172]. Depending on the polarity of the stimulation, tDCS can shift neuronal membrane potentials in a way that slightly increases or decreases the likelihood that neurons will fire in response to synaptic input [173]. These changes in cortical excitability are generally subtle but can influence the responsiveness of neural populations during ongoing cognitive processing [174] and interact with intrinsic local and network-level activity embedded within the nonlinearity of the brain [175].

Given that aging and age-related neuropathology often involve changes in neural excitability [176], tDCS-induced restoration of excitability makes it an attractive option as an intervention. Moreover, the low-intensity profile of tDCS which gently modulates neuronal activity makes it a particularly safe mode for neuromodulation, particularly in clinical contexts [177].

4.1.1 Polarity-specific tDCS

As all tDCS protocols involve the application of current between an anode (inward current) and a cathode (outward current), the placement of these electrodes critically shapes the resulting modulation of neural excitability. In anodal tDCS, the anode is positioned over the target region, whereas in cathodal tDCS, the cathode is placed over the region of interest.

Early seminal work in motor cortex demonstrated that anodal stimulation shifts neuronal membrane potentials toward depolarization, yielding increased excitability at the population level, whereas cathodal stimulation produces the opposite effect, reducing excitability [173,174]. These findings gave rise to the dual-polarity framework, often described as anodal excitation and cathodal inhibition (AeCi) [178]. A substantial body of work supports this polarity-dependent effect, particularly within motor cortex [178]. However, this mapping is less consistent in non-motor regions and during cognitive tasks. In these contexts, the relationship between stimulation polarity and excitability appears more complex, with cathodal stimulation not reliably producing inhibitory effects and, in some cases [178], even enhancing behavioral performance [179]. Accordingly, especially in cognitive domains such as memory modulation, it is advisable to systematically titrate stimulation parameters. This includes testing both anodal and cathodal configurations, as well as varying intensity and task engagement, to determine optimal configurations [180].

4.1.2 Improved precision and effectiveness with tDCS

The variability of tDCS effects is partly attributable to the diffuse current spread associated with conventional electrode montages, which can inadvertently modulate multiple brain regions. To address this limitation, high-definition tDCS (HD-tDCS) approaches employ model-guided placement of multiple smaller electrodes. Computational forward models of head anatomy are used to estimate current flow, and optimization algorithms distribute current across electrodes to maximize focality or intensity at the target site [181,182]. These approaches are increasingly used in both anodal and cathodal protocols and may be particularly valuable for personalized neuromodulation, such as in older adults where anatomical variability may be further pronounced by pathology [183].

Also important for clinical applications is the need to induce changes in cortical excitability that outlast the stimulation period. In addition to immediate effects on excitability, repeated tDCS sessions may produce longer-lasting changes in synaptic plasticity [184]. Experimental studies suggest that stimulation can interact with mechanisms related to long-term potentiation (LTP) and long-term depression (LTD), potentially strengthening synaptic connections within stimulated networks [185]. These plastic changes are particularly relevant for neurorehabilitation contexts, where repeated stimulation sessions may be paired with behavioral training to promote sustained improvements in cognitive function [59,186].

4.1.3 Limitations

Despite its relative simplicity and favorable safety profile, tDCS has several limitations. The absence of a unified model linking stimulation polarity to neural effects necessitates parameter titration, which can impose practical constraints, particularly in clinical and exploratory settings. Moreover, the low intensity of stimulation, while contributing to safety, may limit efficacy and contribute to substantial inter-individual variability [187]. TDCS effects are also state-dependent, interacting with baseline neural activity and ongoing cognitive processes, further complicating reproducibility across individuals [188]. Another significant limitation is its lower penetration depth, with tDCS protocols primarily targeting cortical regions. Although subcortical regions can be indirectly stimulated [189], controlled manipulation of these regions is usually difficult. Finally, its relatively low spatial resolution allows current to spread across cortical regions [190]. Although HD-tDCS improves focality, it remains less precise than other neuromodulation techniques.

4.2 Transcranial Alternating Current Stimulation (tACS)

Transcranial alternating current stimulation (tACS), like tDCS, delivers weak electrical currents via the scalp. However, in contrast to the constant current used in tDCS, tACS applies oscillatory currents that generate electric fields varying periodically over time [191,192]. Rather than primarily shifting baseline excitability, tACS is thought to target a more specific functional substrate: endogenous neural oscillations [180,193]. The theoretical basis for tACS is that externally applied rhythmic stimulation may entrain or synchronize neural oscillations at specific frequencies. When stimulation is delivered at frequencies

that correspond to intrinsic brain rhythms, it may stabilize oscillatory patterns that support information processing [194].

Mechanistically, tACS is proposed to interact with and amplify ongoing neural rhythms, thereby modulating the timing of neuronal depolarization [132]. This temporal modulation can promote more phase-aligned, rhythmic spiking activity, effectively biasing neuronal firing toward particular phases of the oscillatory cycle [132], particularly those that facilitate effective neuronal communication.

Memory processes have been strongly linked to oscillatory activity in several frequency bands. For example, theta rhythms have been associated with hippocampal-cortical communication during memory encoding and retrieval [107,120], while gamma oscillations are thought to support local information processing and the representation of individual memory elements [111,117]. Critically, aging and age-related neuropathology involves a breakdown of these rhythmic dynamics [53,107]. By targeting these rhythms, tACS may influence the temporal coordination of activity across memory-related brain regions, thereby facilitating memory [39].

4.2.1 Power modulation with tACS

One primary application of tACS is the modulation of oscillatory power. When stimulation is applied at frequencies close to intrinsic rhythms, it may reinforce these oscillations through constructive interaction, increasing their amplitude within targeted regions [195]. Because oscillatory activity regulates neuronal excitability [196], strengthening these rhythms may enhance the temporal precision of neural communication.

For instance, older adults often exhibit reduced alpha power in visual cortical regions during tasks requiring suppression of distracting information, contributing to increased susceptibility to interference [125]. TACS can be used to enhance alpha oscillations in these regions, thereby improving distractor resistance, an effect supported by experimental findings [126]. Similar approaches may target reduced theta power during memory maintenance [121] or diminished beta power associated with unsuccessful removal of information from working memory [103].

4.2.2 Cross-frequency coupling modulation with tACS

TACS can also be used to modulate cross-frequency coupling, a key mechanism through which neural activity is coordinated across temporal scales. In such interactions, high-frequency oscillations are nested within specific phases of lower-frequency rhythms [197].These dynamics are thought to support integrative cognitive processes [40], including maintaining separable memory representations [114] and facilitating memory consolidation during sleep [198].

Emerging evidence suggests that memory impairments may arise, in part, from disruptions in these temporally precise coupling relationships [107,199]. Advanced tACS protocols can generate complex waveforms that mimic these coupled dynamics,

allowing experimental manipulation of phase–frequency interactions [40]. Such approaches have been shown to enhance memory performance when stimulation preserves the natural frequency and phase relationships between oscillations [200], representing a promising avenue for age-related cognitive interventions.

4.2.3 Interregional synchrony modulation with tACS

TACS may also enhance communication between distributed brain regions by modulating interregional synchrony. Neural populations across regions often exhibit coordinated oscillatory activity, reflecting aligned periods of heightened excitability that facilitate information exchange [47]. Multi-site tACS protocols, which deliver stimulation to multiple regions simultaneously, can bias oscillations to align in phase and frequency across these regions [40].

This approach has been shown to improve coordination between frontal and temporal regions during memory encoding and retrieval [107]. Notably, aging is associated with reduced synchronization across such networks, and tACS has been shown to partially restore these dynamics [107]. Further investigation of interregional phase synchronization in aging may inform the development of more effective memory enhancement protocols.

4.2.4 Closed-loop modulation with tACS

Recent developments in neuromodulation research have begun investigating closed-loop stimulation approaches, in which stimulation parameters are dynamically adjusted based on ongoing neural activity [201,202]. In principle, such approaches could allow stimulation to be aligned with specific phases of neural oscillations or with particular cognitive states. These may be especially relevant for memory processes, which often depend on precise timing relationships among neural signals [154,200]. By aligning stimulation with endogenous rhythms in real-time, closed-loop protocols may enhance the effectiveness of neuromodulation interventions. Although these approaches are still largely experimental, they represent an important direction for future research in memory neuromodulation.

4.2.5 Limitations

TACS shares several limitations with tDCS including state-dependence [162], low spatial resolution [193] and limited ability to directly target subcortical structures. Although high-definition tACS improves focality, spatial precision remains constrained relative to other neuromodulation techniques. A potential advantage of tACS, however, lies in its frequency specificity: despite broad current spread, its effects may preferentially influence neuronal populations whose intrinsic frequencies match the stimulation frequency. This property may confer a degree of functional specificity, although this hypothesis requires further empirical validation. Frequency specificity also enables personalization of tACS to individual oscillatory dynamics, offering a potential route toward precision medicine. However, estimating individual frequency profiles introduces additional logistical constraints, and emerging evidence suggests that even small deviations from intrinsic frequencies may disrupt rhythmic activity [138], further

underscoring the need for individualized parameter selection. Despite these limitations, tACS is receiving significant interest in enhancing cognitive function in older adults experiencing memory problems [39].

4.3 Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation (TMS) is an established noninvasive brain stimulation method currently used as therapeutic interventions for several psychiatric and neurological disorders, including depression [203] and stroke rehabilitation [204]. The biophysics of TMS is different from that of electrical stimulation methods: TMS involves the application of rapidly changing magnetic fields to induce electrical currents in cortical tissue [205,206]. TMS can be delivered at intensities high enough for the induced current to directly depolarize neurons, making it capable of producing more immediate and focal effects on neural activity [207]. TMS also offers excellent spatial and temporal resolution, and there is considerable control over how multiple TMS pulses are combined. While single-pulse TMS protocols are used to transiently investigate brain function, multi-pulse protocols of different varieties are currently under investigation for memory enhancement.

4.3.1 Repetitive TMS protocols

Repetitive TMS (rTMS) protocols involve the administration of multiple magnetic pulses delivered at a specific frequency for several minutes [208]. RTMS can produce after-effects that depend on the frequency of stimulation and its duration. Specifically, high-frequency stimulation (> 5 Hz) is generally thought to increase cortical excitability, whereas low-frequency stimulation (< 1 Hz) may decrease it [209], although there is substantial interindividual variability in these effects [210].

When rTMS is performed in older adults, some studies have found benefits to associative memory [211,212] and recognition memory [213], some have found enhancements in connectivity among frontoparietal regions with rTMS during encoding, albeit without a change in memory performance [214], while others have not observed any benefits [215]. Given this variability, other studies have sought to pair rTMS with cognitive training in order to enhance stimulation outcomes, with modest success [216,217].

4.3.2 Patterned TMS protocols

Certain TMS protocols use structured pulse patterns rather than simple continuous trains, one of the most prominent being theta-burst stimulation (TBS). TBS consists of bursts of three pulses delivered at 50 Hz, with these bursts repeated at 5 Hz, approximating a theta-frequency temporal structure [218]. Typically, 300–600 pulses are administered over a very short duration, often on the order of tens of seconds, yet can induce changes in cortical excitability that persist for up to approximately 60 minutes [218]. Thus, TBS protocols can achieve the effects of rTMS in a more time-efficient manner [219].

TBS is commonly applied in two main variants. In continuous TBS (cTBS), bursts are delivered without interruption, whereas in intermittent TBS (iTBS), brief pauses are introduced after short trains of stimulation (typically every two seconds). These two protocols are generally associated with opposing aftereffects, with cTBS producing reductions in cortical excitability and iTBS producing increases [218], broadly analogous to the inhibitory and facilitatory effects often attributed to cathodal and anodal tDCS, respectively. Although originally characterized in the motor cortex, emerging evidence suggests that these bidirectional effects extend to other cortical regions as well [220,221].

Given its facilitatory effects, iTBS has been investigated as a potential tool for cognitive enhancement, including in aging populations, with initial studies reporting improvements in memory performance [222]. However, despite these promising findings, the application of patterned TMS protocols such as TBS for cognitive enhancement remains relatively underexplored.

4.3.3 Indirect subcortical TMS protocols

Although TMS primarily affects superficial cortical regions, stimulation of certain cortical sites can influence deeper structures through network connectivity. For example, stimulation of the lateral parietal cortex has been used to modulate activity within hippocampal networks involved in episodic memory [165,166,223–225]. Functional connectivity analyses suggest that such stimulation may influence hippocampal activity indirectly through cortical-hippocampal pathways [165,223–225].

Several studies have reported improvements in episodic memory performance following repeated TMS sessions targeting cortical nodes connected to the hippocampus [226]. These findings have generated interest in the possibility of using network-guided stimulation approaches to enhance memory function, including in older adults [223].

4.3.4 Limitations

While TMS is generally considered safe when applied within established safety guidelines [227], its relatively high stimulation intensity raises concerns regarding rare but possible adverse events, including seizure induction. Although such events are uncommon when protocols are properly followed, they remain the most serious safety consideration associated with the technique [227]. More frequently reported side effects include transient scalp discomfort or pain at the stimulation site, as well as occasional auditory sensations related to coil discharge [227]. A further practical limitation of TMS is that it is primarily restricted to laboratory and clinical environments. Unlike lower-intensity neuromodulation approaches such as tDCS, or implantable systems such as deep brain stimulation (DBS), TMS is difficult to translate into portable or home-based devices that can be safely administered under remote supervision. This constraint limits the feasibility of frequent or self-administered dosing schedules and reduces its accessibility for long-term or high-frequency use in real-world settings.

4.4 Transcutaneous Vagus Nerve Stimulation (tVNS)

Vagus nerve stimulation represents another neuromodulation strategy that may influence memory through engagement of neuromodulatory systems [157]. Traditional vagus nerve stimulation involves implantation of a device that stimulates the cervical vagus nerve, but more recent approaches have explored noninvasive stimulation of vagal afferents, often delivered through electrodes placed on the ear (auricular stimulation) or neck [228].

4.4.1 Mechanisms of action

Stimulation of vagal afferents can activate brainstem pathways that project to several neuromodulatory systems, including the locus coeruleus and basal forebrain [229,230]. These systems release neurotransmitters such as norepinephrine and acetylcholine, which are known to influence attention, arousal, and synaptic plasticity.

Through these pathways, vagus nerve stimulation may indirectly enhance plasticity within hippocampal and cortical circuits that support memory formation [231,232]. Experimental studies have demonstrated that pairing vagus nerve stimulation with behavioral training can strengthen learning-related neural connections [233]. Others reported improvements in associative memory [234,235] or attention [236] following auricular stimulation protocols.

4.4.3 Limitations and translational potential

TVNS is a relatively new technology and there is a need for further studies in humans to explore its benefits to memory enhancement. Although research specifically targeting aging populations remains limited, the mechanistic link between vagal stimulation and neuromodulatory systems involved in learning, and emerging promising evidence [234,237] has generated interest in its potential role in cognitive rehabilitation [238,239].

One advantage of noninvasive vagus nerve stimulation is the possibility of portable or home-based devices, which could make the technology more accessible for long-term therapeutic use. Because vagal stimulation may enhance plasticity mechanisms rather than directly driving neural activity, it may also be particularly well suited for combination with behavioral therapies or cognitive training programs.

4.5 Emerging and Experimental Neuromodulation Techniques

In addition to established stimulation modalities, several emerging technologies are being investigated as potential tools for influencing memory-related neural circuits.

4.5.1 Temporal interference stimulation

Temporal interference stimulation is a relatively new electrical stimulation technique designed to target deeper brain regions by combining multiple high-frequency electrical fields that interact to produce lower-frequency modulation within specific brain locations [240,241]. Recent work shows promise in translating this technology to target deep brain

structures in humans [242,243], including in hippocampus [243], which suggests significant potential for exploring clinical applications in the future.

4.5.2 Transcranial focused ultrasound (tFUS)

Transcranial focused ultrasound uses acoustic energy to influence neural activity in targeted brain regions [244]. Because ultrasound waves can penetrate deeper into the brain than conventional electrical stimulation, tFUS has been explored as a potential method for modulating subcortical structures involved in memory. Research in this area remains early, but initial studies suggest that ultrasound stimulation can influence neural activity and behavior. For instance, animal models find enhancement of synaptic plasticity [245] and reduction of AD-related biomarkers with tFUS [246], suggesting the need for exploring this method in humans.

4.5.3 Sensory entrainment approaches

Another emerging strategy involves sensory stimulation designed to entrain neural rhythms, such as rhythmic visual or auditory stimulation delivered at specific frequencies. For example, visual flicker or auditory tones delivered at gamma frequencies have been investigated as methods for influencing neural oscillations associated with memory processes [247,248]. Although much of this research is still experimental, sensory entrainment approaches offer the advantage of being relatively simple and noninvasive.

Together, these noninvasive neuromodulation techniques represent a rapidly evolving set of tools for influencing neural circuits involved in memory. The following section examines invasive neuromodulation approaches that have also been investigated for modulating memory-related brain systems.

5. Invasive Neuromodulation Approaches

Although noninvasive stimulation techniques have attracted increasing attention for cognitive enhancement, invasive neuromodulation approaches have also provided important insights into the neural circuits that support memory. These methods involve surgically implanted devices that deliver electrical stimulation directly to peripheral nerves or to specific brain regions. Because implanted electrodes can deliver stimulation with greater precision and intensity than noninvasive approaches, they have historically been used in the treatment of neurological disorders such as Parkinson's disease [249], epilepsy [250], and chronic pain [251].

In recent years, invasive neuromodulation has also been explored as a potential strategy for influencing memory-related brain circuits [252]. These studies have been motivated by advances in our understanding of the neural networks that support memory and by the observation that stimulation of certain brain regions can alter cognitive function. Although the clinical use of invasive stimulation for memory disorders remains experimental, research in this area has provided valuable insights into how stimulation may influence learning and memory processes.

5.1 Deep Brain Stimulation (DBS)

Deep brain stimulation (DBS) involves the implantation of electrodes into specific brain regions connected to an implanted pulse generator that delivers electrical stimulation [31,253]. DBS has become an established therapy for movement disorders such as Parkinson's disease [249,254] and essential tremor [255,256], and it is increasingly being investigated for other neurological and psychiatric conditions [33,34].

5.1.1 Targets for memory modulation

Several brain regions involved in memory networks have been explored as potential targets for DBS. One of the most widely studied targets is the fornix, a major white matter tract that connects the hippocampus with other limbic and cortical structures [257–260]. Because the fornix plays a central role in hippocampal memory circuits, stimulation of this pathway has been hypothesized to influence memory function by modulating activity within the broader limbic network [261].

Other potential targets include the entorhinal cortex [262], which provides major input to the hippocampus, and the hippocampus itself [263], a critical structure for episodic memory formation. These regions have been investigated primarily in research settings, often involving patients undergoing neurosurgical procedures for epilepsy or other neurological conditions.

5.1.2 Evidence for memory effects

Research examining the effects of DBS on memory has produced a complex set of findings. Some studies have found improvements in memory with hippocampal stimulation [264,265] while others have found impairments [266]. Others have found benefits with stimulation of the entorhinal cortex [262]. These differences have been attributed to differences in the precise spatial location in the hippocampal and other temporal lobe regions where stimulation is performed [252].

Fornix stimulation has been shown to benefit memories [267], although some studies find inconsistent across individuals, with effects limited to those at a more advanced age [268]. Given the mixed results across studies, larger controlled trials are needed to determine whether DBS can produce clinically meaningful improvements in memory function in neurodegenerative disease.

5.1.3 Clinical considerations

Although DBS provides a powerful tool for modulating neural circuits, its invasive nature limits its widespread application for cognitive disorders. Surgical implantation carries inherent risks, and careful patient selection is required [269]. For this reason, DBS for memory disorders is currently considered an experimental approach and is generally reserved for research settings or for patients already undergoing neurosurgical procedures for other indications.

Nevertheless, DBS research has been valuable for identifying neural circuits that are capable of influencing memory when stimulated. Insights gained from these studies may inform the development of noninvasive neuromodulation techniques that aim to target similar networks.

5.2 Implanted Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is another form of invasive neuromodulation that has been widely used in the treatment of epilepsy and treatment-resistant depression [157]. In conventional VNS therapy, an electrode is surgically implanted around the cervical vagus nerve in the neck and connected to an implanted pulse generator that delivers intermittent electrical stimulation [157].

5.2.1 Mechanisms

The vagus nerve contains extensive afferent projections that transmit sensory information from peripheral organs to the brainstem. Electrical stimulation of vagal afferents activates neurons in the nucleus tractus solitarius, which in turn project to several neuromodulatory systems, including the locus coeruleus and basal forebrain [157]. Activation of these pathways leads to the release of neuromodulators such as norepinephrine and acetylcholine across widespread cortical and hippocampal regions [157]. These neuromodulatory systems play important roles in regulating attention, arousal, and synaptic plasticity [270]. As a result, VNS has been proposed as a method for enhancing learning-related plasticity within memory circuits [271].

5.2.2 Evidence for memory effects

Studies in both animals [232,272] and humans [273,274] suggest that vagus nerve stimulation can influence memory processes. In experimental paradigms, stimulation paired with learning experiences has been shown to enhance memory consolidation and strengthen neural representations associated with learned information. For example, pairing vagal stimulation with sensory [275] or motor [276] training has been shown to facilitate learning-related plasticity in several neural systems.

In human studies, memory effects have been observed in patients receiving VNS therapy for epilepsy [273,277]. Some investigations have reported improvements in aspects of memory performance following chronic stimulation, although findings have varied across studies and individuals [271,278,279]. Importantly, these effects may depend on the timing of stimulation relative to learning events, suggesting that VNS may act by modulating plasticity mechanisms involved in memory consolidation [274].

5.2.3 Clinical relevance for aging populations

Although implanted VNS is not currently used specifically to treat age-related memory decline, its mechanisms of action provide important insights into how neuromodulatory systems can influence learning and memory. The ability of vagal stimulation to engage

widespread plasticity-related pathways has motivated the development of noninvasive vagus nerve stimulation techniques [280], which may offer similar benefits without requiring surgical implantation.

5.3 Ethical and Clinical Considerations

The use of invasive neuromodulation for cognitive enhancement raises several ethical and clinical considerations. Because these procedures involve surgical intervention, the potential risks must be carefully weighed against the expected benefits. For conditions such as Parkinson's disease or epilepsy, where DBS and VNS are already established therapies, the risk–benefit balance may be relatively clear. In contrast, applying invasive stimulation to treat cognitive decline in aging populations presents additional challenges.

Another important issue involves the variability of stimulation effects on memory circuits. Memory processes depend on complex and highly distributed networks, and stimulation may influence these networks in ways that are difficult to predict [252]. In some cases, stimulation can enhance memory, whereas in others it may disrupt normal neural dynamics.

For these reasons, invasive neuromodulation for memory disorders remains largely experimental. Continued research will be needed to better understand which neural targets, stimulation parameters, and patient populations may benefit most from these approaches. Insights gained from invasive studies may also guide the development of safer and more scalable noninvasive neuromodulation strategies for cognitive rehabilitation.

6. Evidence from Clinical Trials

Over the past two decades, a growing number of clinical studies have examined whether neuromodulation can improve memory function in older adults. These studies span a range of stimulation technologies, including transcranial electrical stimulation, transcranial magnetic stimulation, vagus nerve stimulation, and emerging stimulation approaches. While the body of evidence remains heterogeneous, clinical trials have begun to provide important insights into the conditions under which stimulation may influence memory-related cognitive outcomes. Because memory decline occurs across a spectrum, from healthy aging to mild cognitive impairment and Alzheimer's disease, clinical studies have typically examined these populations separately. Differences in baseline neural integrity, disease pathology, and cognitive reserve may influence how individuals respond to neuromodulation interventions.

6.1 Trials in healthy aging

Studies in healthy older adults have primarily focused on short-term experimental interventions to examine whether stimulation can enhance cognitive functions, including memory. Given that healthy individuals have no a priori clinical need for invasive

interventions, much of this evidence is accumulated through noninvasive methods.

A number of studies have examined the effects of tDCS on memory performance in healthy older adults [281,282]. Many studies find benefits with anodal stimulation of prefrontal regions [283,284], while others find benefits with stimulation of temporoparietal regions [285]. Meta-analyses of studies performing tDCS find improvements in working memory [282] and episodic memory [286] of healthy older adults, with stronger improvements occurring with higher intensities and more sessions. Indeed, with tDCS, behavioral effects on memory have been accompanied by measurable changes in neural activity or functional connectivity, suggesting that stimulation may influence the physiological processes supporting memory [186,285,287]. Despite this promise, a recent clinical trial with sample sizes larger than those used in previous studies did not find evidence of improvements in working memory or episodic memory with prefrontal tDCS [288], suggesting the need for further research.

With tACS, several investigations have reported improvements in working memory or associative memory following stimulation protocols designed to target specific oscillatory frequencies [39,107,149,186,289–294]. In some cases, stimulation effects have been accompanied by measurable changes in anatomy [186] and functional activity [107,186,291], suggesting that the intervention may alter underlying neural dynamics. Other protocols have targeted gamma-band stimulation, motivated by evidence linking gamma oscillations to memory encoding and synaptic plasticity [149,295,296]. In animal models, gamma stimulation has been shown to influence amyloid processing and neural activity patterns associated with Alzheimer's disease pathology [297–299]. Although translation of these findings to humans remains ongoing, preliminary studies have begun exploring whether gamma-frequency stimulation may influence cognitive performance or neural network dynamics in aging populations [289,290]. Meta-analytic evidence currently supports modest improvements in cognitive function with tACS in older adults, including on memory function, although the specific effect on memory alone remains to be established [39].

Considering repetitive TMS, meta-analytic evidence does not yet support robust memory enhancement in older adults [300], consistent with the heterogeneous and often inconsistent findings reported in younger populations [301]. One notable exception is the growing evidence that TMS targeting cortical regions functionally connected to the hippocampus can enhance memory. Initial demonstrations [165] have been followed by more recent meta-analytic support [226], with similar effects observed in older adults [223]. This network-targeted approach may therefore represent a particularly promising direction for future research.

6.2 Trials in mild cognitive impairment

Mild cognitive impairment (MCI) represents a particularly important target for neuromodulation interventions because individuals with MCI show measurable memory deficits but may still retain substantial neural plasticity [14]. Several clinical studies have

therefore investigated whether stimulation approaches can improve memory performance or slow cognitive decline in this population.

An early clinical trial in over two hundred individuals with an MCI profile found promising effects for tDCS when combined with working memory training, over and above either intervention individually [302]. Another study suggested a dose-dependent modulation of neural activity with some potential benefits to working memory [59]. There is some evidence to suggest that tDCS paired with cognitive training may support memory function in MCI [303] but several other trials have found only weak effects of the paired intervention, with these effects failing to reach statistical significance [304,305].

A potential reason for this disparity across studies may be that tDCS-cognitive training approach may have utility in a more specific symptom profile. In a large, multisite clinical trial, repetitive prefrontal tDCS paired with cognitive training and yearly boosters suggested stronger benefits in memory for people with both MCI and depression, clinical profiles that both increase the risk of future dementia, than individuals with MCI alone [306]. Although the intervention did not enhance cognitive function, it reduced the degree of decline in cognition over several years, with particular benefits to verbal memory, suggesting a preventative benefit to individuals with this specific symptom profile.

A few studies have also examined other neuromodulation methods. rTMS, administered over ten sessions, has also been shown to prevent the decline in memory performance for at least one month [307]. Theta frequency tACS combined with cognitive training has also been shown to improve short-term memory [308]. Indeed, preliminary meta-analytic evidence finds some evidence in favor of tACS, but there is a need for larger and more standardized clinical trials [309].

6.3 Trials in Alzheimer's disease

Neuromodulation has also been explored as a potential intervention for individuals with Alzheimer's disease, particularly in the early stages of the condition. In these studies, the goal is often to stabilize or modestly improve cognitive function by influencing neural networks that remain partially preserved despite disease-related degeneration. Both invasive and noninvasive stimulation approaches have been investigated in Alzheimer's disease. Noninvasive techniques such as repetitive transcranial magnetic stimulation and transcranial electrical stimulation have been applied to cortical regions involved in memory and language networks.

In a multisite clinical trial involving over a hundred patients, the neuroAD protocol, which includes repetitive TMS over six frontoparietal brain regions over six weeks, was shown to improve cognitive function but only in people with milder AD [310]. When stimulating a single region, rTMS over the dorsolateral prefrontal cortex alone has so far not shown to produce cognitive improvements relative to placebo [311], while that of the precuneus, an important node of the episodic memory network [42], has been successfully shown to prevent further decline in memory through modulation of gamma oscillatory activity [312].

Meta-analytic evidence typically supports the use of rTMS for improving cognitive function, at least in mild-to-moderate AD [313], particularly when TMS targets are personalized [314], suggesting promise in the continued exploration of these interventions in AD.

Several clinical trials have also examined whether tACS can produce cognitive enhancement. Administration of 40 Hz tACS over 15 days has been shown to improve some aspects of memory function along with an improvement in coordination between the two critical theta and gamma band rhythms via phase-amplitude coupling, although the effects were transiently evident only at the end of the intervention but not three months after [315]. Modulation of the same frequency but in precuneus for eight weeks led to clinically significant benefits in memory, along with restoration of cholinergic dysfunction, using a home-based administration protocol [316]. In fact, changes in memory and cholinergic transmission can be transiently observed with just 60 minutes of stimulation in people with AD with gamma frequency tACS over the precuneus [317]. Similar effects have been seen with gamma frequency stimulation over temporal regions, with their repetitive stimulation increasing cerebral perfusion in the affected areas [289]. Thus, gamma frequency tACS is becoming increasingly evident as a protocol for mitigating memory deficits in AD.

Other methods of brain stimulation are also being explored. Transcranial pulse stimulation, a variant of ultrasound stimulation, has recently been shown to have positive effects, with improvements in cognition occurring in relatively younger subgroups of people with AD [318]. Anodal tDCS over temporoparietal regions has also been shown to improve cognitive function [319]. These protocols have been confirmed to at least have a transient effect in meta-analyses as well, although evidence for sustained effects is currently limited [320].

Invasive approaches such as deep brain stimulation targeting the fornix have also been explored in small clinical trials. Early studies suggested that stimulation might influence metabolic activity in memory-related brain networks, although evidence for consistent cognitive improvement remains limited [267]. Other studies have shown that the effects may not be consistent across individuals, and potentially limited to those at a more advanced age [268].

Overall, there appears to be significant promise in exploring techniques like TMS and tACS in AD, motivating the need for larger and more standardized studies. That said, disease-related neurodegeneration may limit the capacity of neural circuits to respond to noninvasive stimulation, particularly in later stages of the disorder. Invasive approaches may hold better promise in such cases, although their benefits would need to be weighed against the significant drawbacks of such methods.

7. Challenges and Limitations

Despite growing interest in neuromodulation as a potential intervention for age-related memory decline, several important challenges remain. These challenges involve both

scientific and practical considerations, including variability in individual responses to stimulation, limitations in targeting memory-related brain circuits, and the difficulty of translating experimental findings into effective clinical interventions. Addressing these issues will be essential for determining the role that neuromodulation may ultimately play in cognitive neurorehabilitation.

7.1 Variability across studies and individuals

One of the most widely recognized challenges in neuromodulation research is the substantial variability in individual responses to stimulation [321]. Across studies, some participants show measurable improvements in cognitive performance following stimulation, whereas others show little or no benefit [188]. In some cases, stimulation may even produce variable outcomes in response to identical stimulation patterns in the same individual [322].

Several factors may contribute to this variability. Differences in brain anatomy can influence how electrical or magnetic fields are distributed within the brain, potentially affecting the extent to which stimulation reaches targeted neural circuits [195]. Age-related changes in cortical thickness, cerebrospinal fluid volume, and brain connectivity may further influence how stimulation interacts with neural tissue [323], leading to higher variability in stimulation outcomes in older adults [324]. In addition, baseline neural activity and cognitive state at the time of stimulation may shape how neural networks respond to external modulation [159,162].

Variability may also arise from differences in disease stage among individuals with mild cognitive impairment or Alzheimer's disease. As neurodegenerative processes progress, structural damage to memory-related circuits may reduce the capacity of those circuits to respond to stimulation. Identifying biomarkers that predict responsiveness to neuromodulation therefore represents an important area of ongoing research [130,325].

7.2 Replicability and heterogeneity of effects

A related challenge concerns the replicability of findings across studies [326]. While many investigations have reported improvements in memory performance following stimulation, results are not always consistent across laboratories or experimental protocols. Differences in stimulation parameters, electrode placement, session duration, and cognitive tasks may all influence outcomes.
Small sample sizes have also been common in early neuromodulation studies, making it difficult to determine whether reported effects generalize to broader populations. As the field matures, larger randomized controlled trials will be necessary to establish more reliable estimates of treatment efficacy and to identify the conditions under which neuromodulation produces meaningful cognitive benefits.

7.3 Magnitude and durability of stimulation effects

Across clinical studies, one of the key questions concerns the magnitude and durability of cognitive improvements produced by neuromodulation. In many trials, reported effects have been modest, and improvements are often measured across broad cognitive outcomes which, when targeting specific memory-related structures, may present an incomplete picture of the effects on memory in the absence of granular tests.

Another important consideration is the duration of stimulation effects. Some studies report improvements that persist for days or weeks following stimulation, particularly when interventions involve repeated sessions [149,306]. However, long-term maintenance of cognitive gains remains an open question. It is possible that sustained improvements may require ongoing or repeated stimulation combined with behavioral training.

7.4 Targeting deep memory circuits

Another challenge involves the difficulty of targeting the neural circuits most directly involved in memory function. Many critical components of memory networks, including the hippocampus and surrounding medial temporal lobe structures, are located deep within the brain [327]. Conventional noninvasive stimulation techniques primarily influence superficial cortical regions, which means that deeper structures must be affected indirectly through network connections.

Although stimulating cortical regions connected to hippocampal networks can influence memory-related activity [165], the precision of this approach can be limited if not supplemented with costly and time-consuming measures of functional connectomes for each individual. Emerging technologies designed to target deeper brain regions, such as temporal interference stimulation or focused ultrasound, may help address this limitation, but these methods remain in early stages of investigation [243].

7.5 Translational gaps between laboratory and clinic

Many neuromodulation studies demonstrating cognitive effects have been conducted under controlled laboratory conditions using relatively short experimental protocols. Translating these findings into clinically meaningful interventions presents several additional challenges [328]. For example, improvements observed in specific cognitive tasks may not always translate into measurable benefits in everyday memory function.

Furthermore, optimal stimulation protocols for therapeutic use remain uncertain. Questions remain regarding the appropriate number of stimulation sessions, the durability of treatment effects, and the most effective ways to combine neuromodulation with behavioral therapies or cognitive training programs [329]. Addressing these issues will require carefully designed clinical trials that evaluate functional outcomes relevant to real-world cognitive performance.

7.6 Safety and regulatory considerations

Although most noninvasive neuromodulation techniques are generally considered safe when used within established guidelines [177,330–334], safety considerations remain important, particularly when interventions are delivered repeatedly or outside of controlled clinical environments. Long-term safety data are still limited for some emerging stimulation technologies.

Regulatory considerations also play an important role in determining how neuromodulation devices can be implemented clinically. Devices intended for therapeutic use must meet regulatory standards for safety and effectiveness, which requires rigorous clinical testing. As the field moves toward more widespread clinical applications, regulatory frameworks will need to balance innovation with patient safety.

Together, these challenges highlight the need for continued research aimed at improving the precision, reliability, and clinical effectiveness of neuromodulation interventions. Understanding and addressing these limitations will be critical for realizing the full potential of stimulation-based approaches in cognitive neurorehabilitation.

8. Future Directions

Advances in neuroscience, neurotechnology, and computational modeling are rapidly expanding the possibilities for neuromodulation-based interventions targeting memory function in aging populations. Although current evidence remains heterogeneous, several emerging directions suggest how neuromodulation may evolve from experimental research tools into more precise and clinically effective therapies.

8.1 Closed-loop neuromodulation

One promising development involves the use of closed-loop neuromodulation systems, in which stimulation parameters are dynamically adjusted based on ongoing neural activity [201,335–338]. Traditional stimulation protocols typically deliver stimulation according to predetermined schedules without considering the moment-to-moment physiological state of the brain. In contrast, closed-loop approaches aim to monitor neural signals, such as electrophysiological activity, and deliver stimulation at specific times when neural circuits are most responsive (e.g., [167,339–342]).

Because memory processes depend heavily on precise timing relationships among neural signals, aligning stimulation with endogenous neural rhythms may enhance the effectiveness of neuromodulation interventions [47]. For example, stimulation delivered at particular phases of ongoing oscillations could potentially strengthen communication between hippocampal and cortical networks involved in memory formation. Indeed, emerging work is beginning to demonstrate the feasibility of this approach, with closed-loop modulation of memory-related theta/gamma rhythms improving neural activity patterns and memory function [343,344]. Although these approaches are still largely in the research stage, advances in wearable sensors and real-time signal processing may make closed-loop neuromodulation increasingly feasible in clinical settings.

8.2 Personalized stimulation protocols

Another important direction involves the development of personalized neuromodulation strategies [206,345–347]. Many current stimulation protocols use standardized parameters applied across individuals, even though substantial differences exist in brain anatomy, neural connectivity, and baseline cognitive function [348]. These individual differences may contribute to the variability in treatment outcomes observed across studies [195].

Personalized stimulation approaches may incorporate neuroimaging [349], electrophysiological recordings [107], or computational modeling [350] to identify optimal stimulation targets and parameters for each individual. For example, structural and functional brain imaging could be used to identify cortical regions most strongly connected to hippocampal memory networks, allowing stimulation to be tailored to the specific network architecture of each patient [223]. The drive for personalization falls under the broader umbrella for adaptive, real-time stimulation protocols capable of achieving precision medicine [351,352].

8.3 Integration with cognitive training

Neuromodulation may be most effective when combined with behavioral interventions that actively engage memory circuits. This expectation is based on the premise that stimulation is most effective when it targets neural structures that are already engaged in a given context [175,353,354]. Indeed, several studies have found such paired interventions to be beneficial for cognitive enhancement [56,58,59]. Emerging evidence further suggests that stimulation paired with cognitive training or learning tasks can produce larger and more durable effects than stimulation delivered in isolation [164]. In these paradigms, stimulation may enhance neural plasticity during periods when relevant circuits are actively engaged [186].

From a neurorehabilitation perspective, this integration is particularly important. Stimulation could potentially be incorporated into structured cognitive rehabilitation programs designed to improve memory strategies, attention, or executive functions that support learning. By facilitating plasticity in neural networks engaged during training, neuromodulation may help reinforce adaptive cognitive processes.

8.4 Home-based and portable stimulation technologies

Recent advances in device design have also opened the possibility of portable or home-based neuromodulation systems (e.g., [316,355,356]). Many noninvasive stimulation techniques rely on relatively simple hardware that could potentially be adapted for supervised home use. Remote monitoring technologies may allow clinicians to track adherence, adjust stimulation parameters, and monitor safety while patients receive stimulation outside of clinical settings [357].

Such approaches could make neuromodulation more accessible for long-term therapeutic use, particularly for individuals with chronic cognitive conditions. While the

available evidence regarding the safety and tolerability of such approaches is promising [356], careful evaluation of safety, usability, and regulatory considerations will be required before home-based stimulation can be widely implemented.

8.5 Integration with neurorehabilitation programs

Ultimately, the greatest clinical impact of neuromodulation may arise from its integration into multimodal neurorehabilitation programs. Rather than serving as a standalone intervention, stimulation technologies may be used to augment established rehabilitation approaches that include cognitive training, physical activity, and behavioral therapies [358].

In this context, neuromodulation could help create neural conditions that promote learning and adaptive plasticity, thereby enhancing the effectiveness of rehabilitation interventions. Continued collaboration among neuroscientists, clinicians, and rehabilitation specialists will be essential for translating neuromodulation research into practical therapeutic strategies that improve memory function and quality of life for older adults.

9. Conclusion

Age-related memory decline represents a major challenge for individuals, families, and healthcare systems as populations continue to age. Although pharmacological treatments for memory impairment have produced limited success, advances in neuroscience have revealed that memory depends on distributed neural circuits whose activity can potentially be influenced through neuromodulation. This insight has motivated growing interest in stimulation-based approaches as tools for enhancing or restoring memory function in older adults.

A variety of neuromodulation techniques, including transcranial electrical stimulation, transcranial magnetic stimulation, vagus nerve stimulation, and emerging technologies such as focused ultrasound, have demonstrated the capacity to influence neural activity within memory-related networks. Early clinical studies suggest that these approaches can sometimes produce modest improvements in memory performance, particularly when stimulation is paired with active learning or cognitive training.

At the same time, the field faces important challenges, including variability in treatment response, limitations in targeting deep memory circuits, and the need for larger and more rigorous clinical trials. Addressing these challenges will require continued advances in stimulation technologies, improved methods for identifying optimal stimulation targets, and closer integration between neuromodulation and established neurorehabilitation strategies.

As these developments progress, neuromodulation may become an increasingly important component of interventions aimed at supporting cognitive health and preserving memory function in aging populations.

Figures

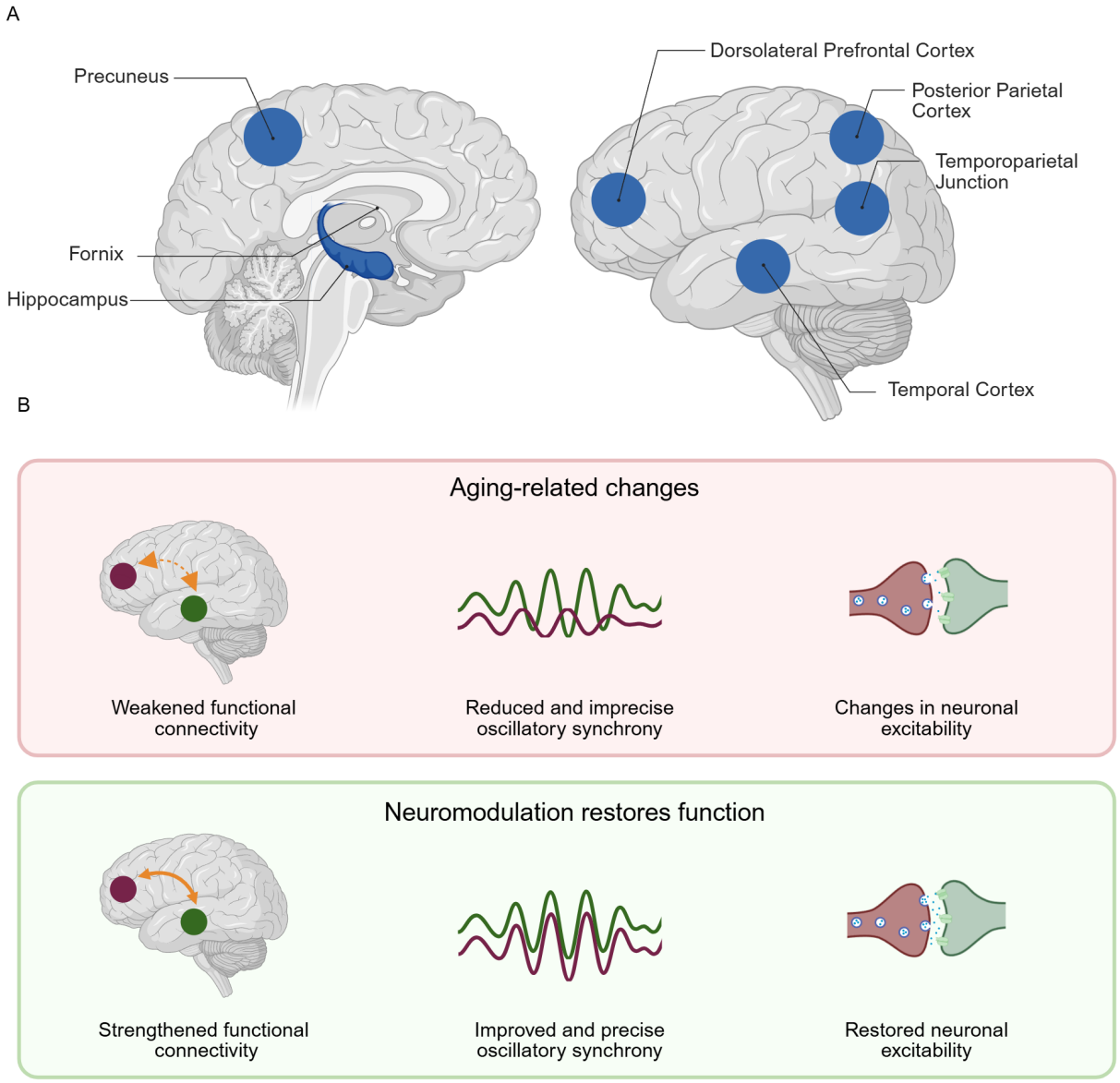


Fig. 1. Targets and mechanisms for memory enhancement via neuromodulation. A. Canonical brain regions typically targeted in neuromodulation studies for memory enhancement in healthy and pathological aging. **B.** Neural mechanisms affected by aging and their remediation with neuromodulation.

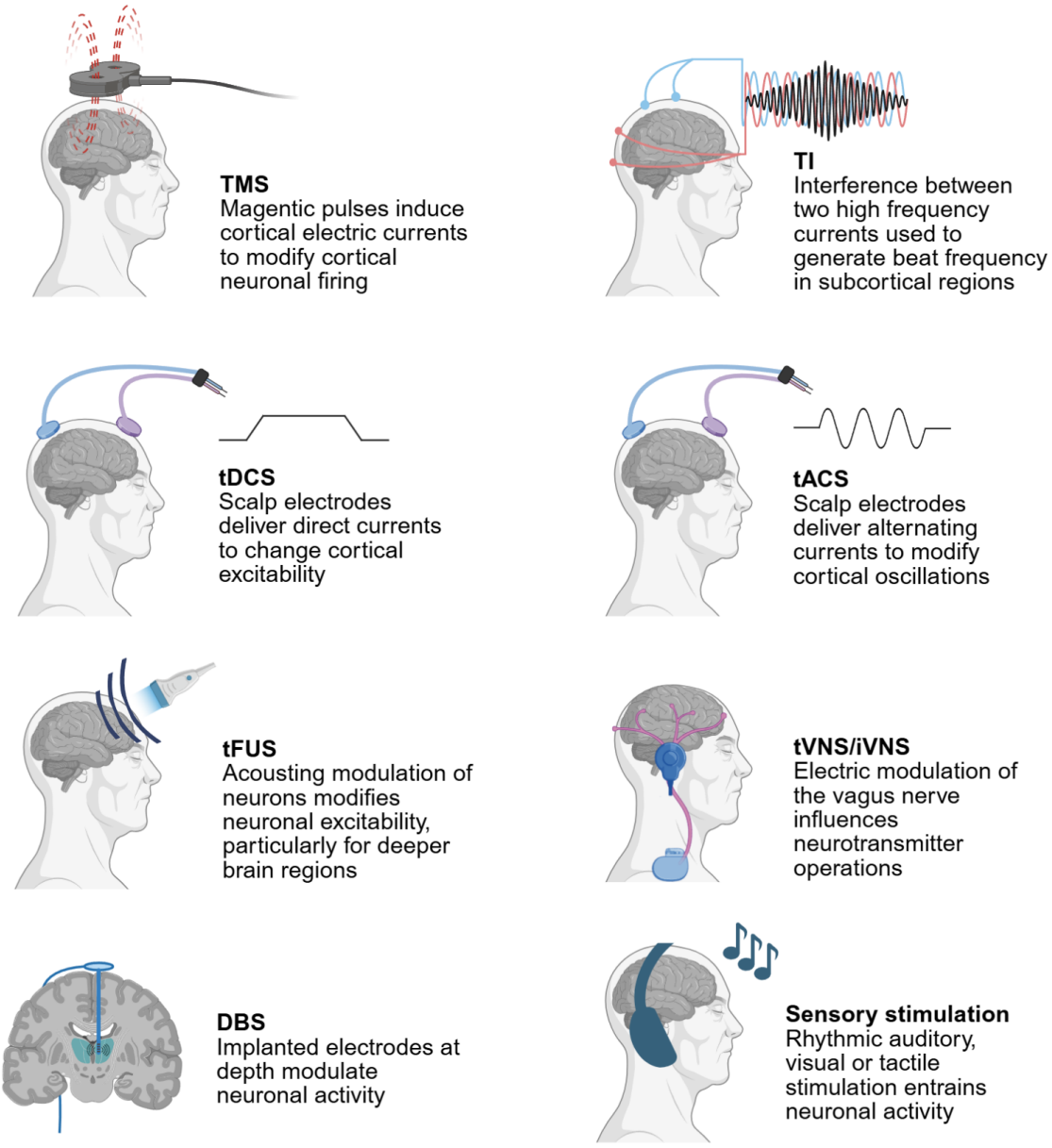


Fig. 2. Neuromodulation Methods. Schematic depicting several invasive and noninvasive neuromodulation methods and their primary effects in the brain. TMS, transcranial magnetic stimulation; TI, temporal interference stimulation; tDCS, transcranial direct current stimulation; tACS, transcranial alternating current stimulation; tFUS, transcranial focused ultrasound stimulation; tVNS/iVNS, transcutaneous/invasive vagus nerve stimulation; DBS, deep-brain stimulation.

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