Journal of Alzheimer's Disease Reports 8 (2024) 241–255
DOI 10.3233/ADR-230115
IOS Press



Review

# Nonmedication Devices in Development for the Treatment of Alzheimer's Disease

Tamara Sleem[a], Boris Decourt[b] and Marwan N. Sabbagh[a,*]
[a]*Department of Neurology, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA*
[b]*Department of Pharmacology and Neuroscience, Texas Tech University Health Sciences Center, School of Medicine, Lubbock, TX, USA*

Received 25 August 2023
Accepted 13 January 2024
Published 16 February 2024

**Abstract**. Huge investments continue to be made in treatment for Alzheimer's disease (AD), with more than one hundred drugs currently in development. Pharmacological approaches and drug development, particularly those targeting amyloid-β, have dominated the therapeutic landscape. At the same time, there is also a growing interest in devices for treating AD. This review aimed to identify and describe devices under development for AD treatment. In this review, we queried the devices that are in development for the treatment of AD. PubMed was searched through the end of 2021 using the terms "device," "therapeutics," and "Alzheimer's" for articles that report on devices to treat AD. Ten devices with 31 references were identified as actively being developed for the treatment of AD. Many of these devices are far along in development. Device-based therapies are often overlooked when evaluating treatment approaches to AD. However, many devices for treating AD are in development and some show promising results.

Keywords: Alzheimer's disease, clinical trials, devices, treatment

## INTRODUCTION

More than 6 million individuals in the United States have Alzheimer's disease (AD), and this number is predicted to increase to 13 million by 2050 [1]. Because the life expectancy of the general population has increased in the past decades to more than 80 years, it is alarming that AD is increasingly prevalent among older individuals, with 72% of those diagnosed with AD dementia being 75 years old or older [2]. The primary symptoms of AD include deficits in short-term and long-term memory, loss of executive function, and several psychiatric symptoms, and the course of the disease eventually leads to premature death [3]. The hallmarks of the brain pathology of AD are extracellular senile plaques composed of amyloid-β (Aβ) peptides, intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau proteins, and central inflammation. Over time, these entities contribute to the neurodegenerative process that leads to the characteristic brain atrophy observed in individuals with AD [1].

*Correspondence to: Marwan N. Sabbagh, MD, Neuroscience Publications, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, 350 W. Thomas Rd., Phoenix, AZ 85013, USA. Tel.: +1 602 406 3593; Fax: +1 602 406 4104; E-mail: Neuropub@barrowneuro.org.

As of January 25, 2022, 143 pharmacological agents were in 172 clinical trials for AD. These pharmacological agents included 31 agents in 47 phase 3 trials, 82 agents in 94 phase 2 trials, and 30 agents in 31 phase 1 trials. Disease-modifying therapies represented 83% of the total number of pharmacological agents in trials, which mainly targeted Aβ and abnormal tau; symptomatic cognitive enhancing treatments represented 10% of these agents; and drugs for the treatment of neuropsychiatric symptoms represented 6.9% of these agents [4].

In addition to pharmacological and behavioral interventions, electromagnetic devices are being investigated to treat AD. To the best of our knowledge, this is the first review to summarize this growing body of literature. These devices employ techniques to identify predetermined regional targets, and they use different mechanisms of action to achieve therapeutic effects. Most device-related strategies focus on ameliorating cognitive symptoms rather than on modifying the disease.

## METHODS

In this study, we reviewed the devices that are currently being investigated for the treatment of AD. We queried the devices that are in development for the treatment of AD. PubMed was searched through the end of 2022 using the terms "device," "therapeutics," and "Alzheimer's" for articles that report on devices to treat AD. Because of institutional accessibility, PubMed was the only database accessed. An overview of these methods and the 10 devices identified is presented in Table 1 (noninvasive devices) and Table 2 (invasive devices) [5–36], and additional information is provided in the text. We have divided the devices into two categories: 1) noninvasive tools that are applied externally, and 2) invasive techniques that require surgery for the internal implantation of electrodes that are connected to external or subcutaneous battery-powered stimulators that can be fine-tuned by expert physicians in a precision medicine context.

## NONINVASIVE TECHNIQUES

### *Repetitive transcranial magnetic stimulation*

Transcranial magnetic stimulation (TMS) is a noninvasive technique that uses a coil positioned against the scalp to briefly apply an oscillating magnetic field (up to 2 Tesla) to a focal area of the brain [37]. It has been suggested that the magnetic field conducts an electric current 2 to 3 cm into the cranium perpendicular to the coil that can depolarize neurons within the targeted stimulation site [38]. Consequently, TMS may promote neuroplastic changes in the brain via several mechanisms, such as modulation of the levels of excitatory and inhibitory neurotransmitters [39], induction of gene expression [40], decrease in the resting motor threshold [41], and modification of the widespread excitability of the sensorimotor system [42]. TMS can be delivered via either high frequency ($\geq$10 Hz) or intermittent theta-burst stimulation to excite cortical tissues, or via either low frequency ($\leq$1 Hz) or continuous theta-burst stimulation (3.5–7.5 Hz) to inhibit neuronal activity [43]. Single-pulse TMS has been well researched for its use in treating migraine [44]. In contrast to single-pulse TMS, patterned repetitive TMS delivers a series of pulses repetitively and rhythmically. Unlike single-pulse TMS, it has long-lasting effects that can induce neuroplastic changes in the brain [45], and it is therefore preferred for the treatment of chronic neurodegenerative conditions that affect memory.

Repetitive TMS (rTMS) commonly targets the left, right, or bilateral dorsolateral prefrontal cortex (DLPFC), the right inferior frontal gyrus, or temporoparietal regions [46], Stimulation of the DLPFC and temporoparietal regions targets memory circuits to improve memory function. Stimulation of the right inferior frontal gyrus target is intended to improve executive function. Significant improvement in cognitive function has been found in studies of both single and multiple sessions of rTMS. For example, rTMS was found to improve both short-term and long-term (4–12 weeks later) cognitive functions [46]. Another studied treatment strategy involves rTMS coupled with cognitive training exercises. This strategy is based on the hypothesis that rTMS serves as a primer that later induces neuroplastic changes [10, 11]. This method was found to have therapeutic value among patients with mild AD compared to patients on standard of care therapy [11]. Although this technique only targets superficial brain areas, its modulatory effects have been detected in deeper brain regions, likely due to the stimulation of interconnected networks [47].

rTMS is currently being used to treat neuropsychiatric diseases such as medication-resistant depression [48]. Potential applications of rTMS to treat AD are being investigated. Animal models in mice have shown that both high frequency [49] and low

Table 1
Summary of studies on noninvasive devices for the treatment of Alzheimer's disease

| Source | Methods | Study Subjects | Outcome Measures and Results |
|---|---|---|---|
| *Repetitive Transcranial Magnetic Stimulation* | | | |
| Cotelli et al., 2011 [5] | Stimulated left DLPFC for 10 sessions over 2 weeks. Follow up testing at 8 weeks. | 10 subjects, 5 in treatment group and 5 in sham group. Mean baseline MMSE 16.1. | MMSE, IADL:<br>Improved language function. |
| Ahmed et al., 2012 [6] | Stimulated bilateral DLPFC for 5 daily sessions. One treatment arm stimulated at 20 Hz. Second treatment arm stimulated at 1 Hz. | 45 subjects, 30 in treatment group divided into 2 treatment arms, 15 in sham group. Mean baseline MMSE 13.8. | MMSE, GDS, IADL:<br>Improved cognitive function that was maintained for 3 months. |
| Rabey et al., 2013 [7] | Stimulated at Broca, Wernicke, bilateral DLPFC, bilateral pSAC for 6 weeks of 5 sessions per week and 12 weeks of 2 sessions per week. | 16 subjects, 7 in treatment group and 8 in sham group. Mean baseline MMSE 22.0. | ADAS-Cog, CGIC, NPI:<br>Improved cognitive function and NPI. |
| Wu et al., 2015 [8] | Stimulated left DLPFC with low-dose antipsychotic medications for 20 sessions over 4 weeks in comparison to low-dose antipsychotic medications alone. | 52 subjects, 26 in treatment group and 26 in sham group. Mean baseline MMSE 15.3. | ADAS-Cog, BEHAVE-AD, TESS:<br>Improved cognitive function, behavior, and psychological symptoms. |
| Lee et al., 2016 [9] | Stimulated Broca, Wernicke, bilateral DLPFC, bilateral pSAC for 30 sessions over 6 weeks. | 26 subjects, 18 in treatment group and 8 in sham group. Mean baseline MMSE 22.5. | ADAS-Cog, MMSE, GDS, CGIC:<br>Improved cognitive function, especially memory and language. |
| Nguyen et al., 2017 [10] | 5 weeks of NeuroAD procedure: cognitive training and rTMS (5 days/week). Evaluated at the end of treatment and 6 months after. | 10 patients with probable AD. | MMSE: no significant correlation with subject outcome.<br>ADAS-Cog: improved at the end of treatment and returned to baseline at 6 months.<br>Improved apathy and dependence scores at both time points. |
| Sabbagh et al., 2020 [11] | Participants randomized to 6 weeks of NeuroAD therapy plus SOC or sham treatments plus SOC. | 131 subjects unmedicated for AD, or on stable doses of acetylcholinesterase inhibitor and/or memantine, MMSE 18–26. | Baseline ADAS-Cog score $\leq 30$ ($\sim$85% of study population) showed a statistically significant benefit favoring active over sham. |
| *Transcranial Direct Current Stimulation* | | | |
| Boggio et al., 2009 [12] | 3 sessions of anodal tDCS in the left DLPFC, temporal cortex performed. | 10 subjects diagnosed with AD, 5 received sham treatment. | VRM task, Stroop task:<br>Improved visual recognition memory. No changes in attention. |
| Bystad et al., 2017 [13] | Daily stimulation for 8 months. | 1 subject case study with early onset AD. | Neuropsychological assessments at 5 and 8 months:<br>Improvements in immediate and delayed recall. Stabilized cognitive functions. |
| Im et al., 2019 [14] | Daily stimulation of the DLPFC for 6 months. | 17 subjects with early onset AD, 7 received sham treatment. | Neuropsychological assessment at 6 months, FDG-PET, MMSE, Boston Naming test:<br>Preserved rCMRglc in the left middle/inferior temporal gyrus. Improved global cognition and language function. |

(*Continued*)

Table 1
(*Continued*)

| Source | Methods | Study Subjects | Outcome Measures and Results |
|---|---|---|---|
| Khedr et al., 2019 [15] | 10 sessions of anodal tDCS of left and right temporoparietal region. | 46 subjects with probable AD, 23 received sham treatment. | MMSE, clock drawing test, MoCA, Cornell Scale for Depression in Dementia, Serum tau, $A\beta_{1-42}$, lipid peroxidase: Improved cognitive function in all measures. No change in serum tau or lipid peroxidase. Increased $A\beta_{1-42}$. |
| Smirni et al., 2021 [16] | Single session of cathodal tDCS to left or right DLPFC. | 40 subjects with mild AD, 20 in control group. | Neuropsychological assessment at baseline, verbal fluency tasks before and after stimulation: Improvement in subjects stimulated over the right DLPFC. |
| *Transcranial Alternating Current Stimulation* | | | |
| Bréchet et al., 2021 [17] | Pilot study for home-based tACS over 4 weeks of 5 days/week, with MoCA testing every 2 weeks. | 2 patients with AD with MoCA > 26. | MoCA: Improved cognition and qualitative improvement in ADLs. |
| Sprugnoli et al., 2021 [18] | Open-label study of daily tACS for 2 or 4 weeks primarily targeting the temporal lobe. | 15 subjects with mild to moderate AD. | ADAS-Cog, MMSE, MoCA, ADL, perfusion-sensitive MRI, EEG: Improved episodic memory. Increased blood perfusion in bilateral temporal lobes with corresponding and spectral power changes in the gamma band. |
| Benussi et al., 2022 [19] | γ-tACS targeting the precuneus for one session. One week later, stimulation inverted. TMS protocol assessed short-latency afferent inhibition in each session. | 60 subjects with AD, 30 received sham treatment. | EEG in 10 patients, RAVLT, face-name associations: Increased gamma frequencies in posterior regions. Increased short-latency afferent inhibition. Improved immediate and delayed recall. Improved face-name associations. |
| *Photobiomodulation Stimulation* | | | |
| Saltmarche et al., 2017 [20] | Case series of weekly transcranial-intranasal PBM and daily intranasal PBM for 12 weeks. | 5 subjects with mild to moderate cognitive impairment. | MMSE, ADAS-Cog: Improved cognitive function. Behavior and sleep qualitative improvement |
| Nagy et al., 2021 [21] | 12 weeks of low-level laser therapy and moderate intensity aerobic exercise. | 60 subjects with anemia and mild cognitive dysfunction, 30 received sham treatment. | MoCA, QOL-AD, Berg Balance Scale, BMI, hemoglobin level: Improved cognitive function, QOL, and balance. Increased hemoglobin levels and reduced BMI. |

| | | | |
|---|---|---|---|
| *Ultrasound Stimulation* | | | |
| Beisteiner et al., 2020 [22] | Single ultrashort ultrasound pulse session. | 35 subjects with AD, sham-controlled. | Preclinical results: Neuropsychological tests improved for up to 3 months after treatment, functional MRI showed upregulation of memory network. |
| *Auditory Stimulation* | | | |
| University Hospital, Tours, 2020 [23] | Proof of concept clinical trial in progress. | Subjects with AD and MMSE > 23. | Memory task of word matching, ecological memory task, the McNair and Kahn Scale, PSQI, HAMA, MADRS: No results currently available. |
| *Transcranial Electromagnetic Treatment* | | | |
| Arendash et al., 2019 [24] | Daily home treatment for 2 months by caregivers. Evaluated at baseline, end of treatment, and 2 weeks after treatment completion. | 8 subjects with mild or moderate AD. | Improved cognitive outcomes on RAVLT and ADAS-Cog: Improved biomarker outcomes on CSF antibodies, p-tau, plasma oligomeric antibodies, and unchanged on FDG-PET. |
| Arendash et al., 2022 [25] | Extended above study for 2.5 years. | Same as above. | No decline in any neuropsychological measures studied. Decreased CSF levels of C-reactive protein, p-tau217, $A\beta_{1-40}$, and $A\beta_{1-42}$. |
| *Gamma Frequency Sensory Stimulation* | | | |
| Chan et al., 2022 [26] | Phase 1 and Phase 2a trials. | NC and AD subjects. | Well tolerated. Entrainment successful, precognitive effects demonstrated. |

AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; ADL, activities of daily living; Aβ, amyloid-β; BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease Rating Scale; BMI, body mass index; CGIC, Clinical Global Impression of Change scale; CSF, cerebrospinal fluid; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalogram; FDG-PET, 18F-fluoro-2-deoxyglucose positron emission tomography; GDS, Geriatric Depression Scale; HAMA, Hamilton Anxiety Scale; IADL, Instrumental Activities of Daily Living; MADRS, Montgomery-Asberg Depression Rating Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; NC, neuropathologic change; NPI, Neuropsychiatric Inventory; PBM, photobiomodulation stimulation; pSAC, parietal somatosensory association cortex; PSQI, Pittsburgh Sleep Quality Index; QOL-AD, Quality of Life in Alzheimer's Disease Scale; RAVLT, Rey Auditory Verbal Learning Test; rCMRglc, regional cerebral metabolic rate for glucose; rTMS, repetitive transcranial magnetic stimulation; SOC, standard of care; tACS, transcranial alternating current stimulation; TESS, Treatment Emergent Symptom Scale; TMS, transcranial magnetic stimulation; VRM, Visual Recognition Memory.

Table 2
Summary of studies on invasive devices for the treatment of Alzheimer's disease

| Source | Methods | Study Subjects | Outcome Measures and Results |
|---|---|---|---|
| *Deep Brain Stimulation* | | | |
| Laxton et al., 2010 [27] | Continuous stimulation of the fornix/hypothalamus for 12 months. | 6 subjects with mild AD. | ADAS-Cog, MMSE, PET:<br>Early reversal of impaired glucose utilization in temporal and parietal lobes.<br>Slowed rate of cognitive decline. |
| Smith et al., 2012 [28] | Open-label trial of continuous DBS of the fornix for 12 months. | 5 subjects with mild, probable AD. | ADAS-Cog, QOL-AD, PET:<br>Increased cerebral glucose metabolism correlated with better outcomes of global cognition, memory, and quality of life. Slowed decline of cognitive function and quality of life |
| Fontaine et al., 2013 [29] | Bilateral DBS of the fornix for 12 months. | 1 subject with mild AD. | MMSE, ADAS-Cog, Free and Cued Selective Reminding Test, PET:<br>Stable cognitive function, increased mesial temporal lobes metabolism. |
| Kuhn et al., 2015 [30] | Continuous low-frequency DBS of bilateral nucleus basalis of Meynert for 4 weeks with 11-month follow-up. | 6 subjects with mild-moderate AD, sham-controlled. | ADAS-Cog, EEG, FDG-PET:<br>Stable cognitive outcomes. |
| Lozano et al., 2016 [31] | Continuous DBS of bilateral fornix-a major fiber bundles for 12 months. | 42 subjects with mild AD.<br>21 sham. | ADAS-Cog 13, CDR-SB, FDG-PET:<br>Patients < 65 possible worsened outcome. |
| Ponce et al., 2016 [32] | ADvance trial, bilateral fornix DBS. | 42 patients with mild, probable AD (mean age 68.2 [7.8] y, range 48.0-79.7 y, 23 men and 19 women). | Patients > 65 improved cognition, increased cerebral glucose metabolism. |
| McMullen et al., 2016 [33] | Case report of above study. | 48-year-old with early onset AD. | Bilateral asymptomatic encephalomalacia at cortical entry sites of leads. |
| Leoutsakos et al., 2018 [34] | Extension of above study for 2.5 years of active group, and 1 year sham with 1 year active of sham group. | 42 subjects with mild AD, 21 received sham treatment. | Favorable safety profile.<br>No difference in treatment arms.<br>Possible benefit among older participants. |
| *Vagus Nerve Stimulation* | | | |
| Sjögren et al., 2002 [35] | Open-label pilot study. Implantation of vagus stimulator (NeuroCybernet Prosthesis) with VNS initiated 2 weeks after implantation. Followed for 6 months. | 10 subjects diagnosed with AD. | ADAS-Cog, MMSE, MADRS, CT, lumbar puncture with CSF analyses:<br>Well-tolerated with improvements in cognitive outcomes. |
| Merrill et al., 2006 [36] | Above study extended to 12 months. | 17 subjects with AD. | Patients were stable or improved from baseline per cognitive outcomes.<br>Reduction of CSF tau and increase in phospho-tau. |

AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes; CSF, cerebrospinal fluid; CT, computed tomography; DBS, deep brain stimulation; EEG, electroencephalogram; FDG-PET, 18F-fluoro-2-deoxyglucose positron emission tomography; MADRS, Montgomery-Asberg Depression Rating Scale; MMSE, Mini-Mental State Examination; PET, positron emission tomography; QOL-AD, Quality of Life in Alzheimer's Disease Scale; VNS, vagus nerve stimulation.

frequency [50] rTMS can improve hippocampal functions linked to learning and memory. A meta-analysis by Chou and colleagues found improved memory functions in patients with AD treated with high frequency rTMS in the left DLPFC combined with low frequency rTMS in the right DLPFC [46]. Some studies have also shown improved executive functioning when the right inferior frontal gyri of patients with mild cognitive impairment or AD are stimulated with high frequency rTMS [46]. Another meta-analysis that investigated the use of high-frequency rTMS in patients with mild AD found significant improvements in cognitive function compared to sham treatment [51]. However, the study found no significant improvement on the Mini-Mental State Examination (MMSE) and no improvement in mood on the Geriatric Depression Scale. Similar studies have also found no significant improvement in instrumental activities of daily living [5–9, 51].

Based on the current literature, it is our opinion that rTMS has the potential to improve cognitive function in AD. However, additional rigorous investigations are necessary to determine whether this treatment can significantly improve quality of life and long-term health outcomes in these patients. Possible drawbacks to this treatment method include adverse effects such as headaches, scalp pain, syncope, transient psychiatric symptoms, and a risk for seizure [52], although rTMS has consistently been found to be safe and well-tolerated by patients overall. Of note, rTMS has been shown to be less effective in patients concurrently taking N-methyl-D-aspartate (NMDA) receptor antagonists such as amantadine [53], further suggesting that the therapeutic action of rTMS involves neuroplastic mechanisms.

*Transcranial direct current stimulation*

Transcranial direct current stimulation (tDCS) delivers weak electrical currents via sponge electrodes soaked with a saline buffer placed on the scalp in precise locations [54]. This method typically delivers a small electrical current (usually 1–2 mA) in a radial pattern that passes through the skull. It can be applied either via anodal stimulation to increase cortical excitability or via cathodal stimulation to decrease neuronal activity, although the modulation of the neuronal activity can vary based on the brain regions targeted and their preponderant neurotransmitters (i.e., excitatory or inhibitory) [43, 54]. tDCS can be applied from a simple compact device that is portable, safe, and inexpensive. It can be self-administered by patients themselves in their home [14], although there is a mild risk of skin lesions from the electrodes, as well as the possibility of dizziness and headaches [43]. A compelling point is that the effects of tDCS on cognitive function as measured by motor cortical excitability were enhanced by partial NMDA agonists, such as d-cycloserine. In addition, similar to rTMS, tDCS had limited effects in patients concurrently taking NMDA antagonists [55]. Overall, tDCS has been shown to be safe, even in longitudinal regimens [14].

Several studies have indicated that tDCS may improve global cognition [12, 14, 56, 57], recognition memory [12], verbal fluency [14, 16], executive function [14], and depression [15] in patients with AD. Interestingly, a single session of tDCS in the area of the left DLPFC in AD patients demonstrated enhanced recognition memory [12]. Notably, after ten sessions of tDCS over bilateral temporoparietal regions, it was observed that patient scores on cognitive and depression scales were improved, and these improvements correlated with an increase in plasma $A\beta_{42}$ compared to a sham-treated group [15]. In patients with AD, the plasma levels of $A\beta_{42}$ are generally lower in comparison to healthy individuals, making it a useful biomarker of this disease [15]. Patients who self-administered tDCS for 6 months showed significant improvements in global cognition, language, and stabilized glucose metabolism in the left middle/inferior temporal gyrus [14]. Patients' executive function and attention remained stable; however, there were no differences in delayed recall performance between the tDCS treatment group and the sham treatment group [14]. Moreover, an AD case study reported by Bystad et al. showed that daily tDCS use for 8 months resulted in improved memory and stabilized cognitive decline [13]. A meta-analysis of 27 randomized-control trials comparing tDCS to rTMS in AD and mild cognitive impairment subjects found a significant improvement in global cognition in AD, but no significant difference in participants with mild cognitive impairment [57]. This finding suggests that the effects of these methods maybe more adapted to mild stages of AD rather than early stages, though the potential cognitive benefits in patients with mild cognitive impairment could be partly masked by the use of cognitive scales not sensitive enough to detect small improvements. Noticeably, patients in the rTMS-treated groups showed greater improvement in global cognition than the patients in the tDCS-treated groups [57]. Overall, tDCS is a potentially effective, portable, and safe noninvasive

external stimulation technique that seems to be most efficient in treating patients with mild-to-moderate AD.

*Transcranial alternating current stimulation*

Transcranial alternating current stimulation (tACS) uses low amplitude alternating electrical currents applied outside the skull to modulate brain oscillations in selected brain regions. It can selectively enhance theta or gamma oscillations [58]. This technique is suspected to function by increasing synaptic plasticity, and the effects are long lasting [59]. It can be administered either during cognitive tasks ("online tACS") or before or between cognitive tasks ("offline tACS"). However, further research is needed to determine the optimal method of administration for clinical benefits [60].

In a clinical trial setting, a single session of gamma-frequency tACS resulted in improvements in immediate and delayed recall memory in AD patients compared to a sham-treated group [19]. It has also been found to significantly increase blood perfusion bilaterally in the temporal lobes on positron emission tomography, which correlated with improvement in episodic memory [18]. A pilot study using a home-based tACS paradigm on two AD patients suggested potential memory enhancement when stimulating the left angular gyrus and the potential feasibility of this technique [17]. As with tDCS, initial research of tACS has been shown to be safe, portable, inexpensive, and potentially effective in the treatment of AD; however, additional investigations are needed to demonstrate clinical utility.

*Photobiomodulation stimulation*

Photobiomodulation stimulation (PBM) works by using light-emitting diodes to transcranially or intranasally emit low levels of red or near-infrared light to modulate neural oscillations [61]. It has also been referred to as low-level light therapy. It is currently being explored in the treatment of dementia [62], traumatic brain injury [63], stroke [63], Parkinson's disease [64], and other neurological conditions. In a review of PBM on animal models using mice and rats with AD [65], PBM has been found to reduce the accumulation of Aβ [66–69], improve cognitive function [66, 67, 69, 70], reduce inflammatory response and oxidative stress [66, 68, 70, 71], and enhance mitochondrial function [66, 68, 70]. Unfortunately, many different paradigms are used in a large number of studies, making it difficult to objectively compare the results and determine the optimal methods for clinical practice. Nonetheless, transcranial infrared brain stimulation is becoming the preferred method of PBM for AD because it has been shown to lead to improved cognition and emotional states [72].

In a case series reported by Saltmarche et al. [20], five patients with mild-to-moderate AD were treated for 12 weeks with a combination of weekly transcranial-intranasal PBM delivered in the clinic and daily intranasal PBM delivered in the patients' homes. Patients showed significant improvement in subjective symptoms such as sleep, anger, and anxiety and objective improvement in cognitive function. No adverse effects caused by the treatment were observed [20]. Some protocols have also studied the benefits of using PBM in conjunction with aerobic exercise therapy in patients with AD and anemia [21]. It was reported that the use of these two therapies together induced a significant improvement in cognitive functions and quality of life compared to aerobic exercise alone [21]. Thus, clinical trials suggest that PBM may be a valuable treatment option for patients with AD.

*Ultrasound stimulation*

Ultrasound stimulation of the brain has been found to effectively and precisely deliver excitatory or inhibitory stimuli to specifically targeted brain regions [73]. It can be applied using many different settings, such as high-intensity or low-intensity ultrasound. High-intensity stimulation creates permanent focal lesions in the brain, whereas low-intensity waves excite or inhibit areas of the brain reversibly [73]. Other methods of ultrasound stimulation include transcranial pulse stimulation (TPS) [22] and transcranial focused ultrasound stimulation [74]. Research for these two treatment modalities appears promising for movement disorders; however, more exploration is needed to determine their potential in cognitive disorders, including the refinement of administration methods, safety profiles, and efficacy [75].

In a clinical trial using TPS, which uses very short ultrasound pulses to stimulate brain regions, 35 patients with AD were treated for 2 to 4 weeks and had significant improvements in cognitive function that lasted up to 3 months. Functional magnetic resonance imaging data showed corresponding memory network upregulation after treatment [22].

*Auditory stimulation*

Various types of auditory stimulation, such as white and pink noises, are being explored for their effects on sleep and memory disturbances [76]. Positive outcomes have been noted, although more evidence is needed [76]. One study of pink noise in cognitively normal older adults has observed significantly improved word recall in comparison to sham-treated groups [77]. The same investigators went on to study pink noise in patients with mild cognitive impairment and showed a similar improvement in morning word recall [78]. Based on this pilot concept, a clinical trial was started to determine whether pink noise may help improve memory consolidation and retention in patients with AD, although results have not yet been published [23].

*Transcranial electromagnetic treatment*

Transcranial electromagnetic treatment (TEMT) uses perpendicular magnetic and electric waves emitted from a transducer. Compared to previous methods, TEMT is capable of acting on the main AD pathologies by disaggregating Aβ and p-tau oligomers, as well as enhancing brain mitochondria [24, 79–81]. TEMT has been studied using the MemorEM device by NeuroEM Therapeutics, Inc. under clinical trial settings. This device has the advantage of being portable and can thus be administered by the patients' caregivers in their homes for daily treatment regimens [24]. In a phase 2 pilot trial over a 2-month period, no subjective or objective adverse effects were noted in the eight AD subjects that used the device twice daily [24]. Given the positive initial results, this trial was extended for a total time period of 2.5 years [25]. Cognitive functions in these patients were stabilized without further decline during that period. Cerebrospinal fluid analysis showed reduced levels of p-tau-217, $A\beta_{40}$, $A\beta_{42}$, and C-reactive protein. No adverse effects were observed with the extended treatment [25]. In summary, the extended trial found that TEMT is generally safe, enhances cognitive functions, and stabilizes brain functions overall [24, 25].

*Gamma frequency sensory stimulation*

The role of gamma brain activity (approximately 25–100 Hz) in cognitive function, including memory, is well known, and it is fundamental for healthy brain activity and intrabrain communication. Electrically, AD is characterized by reductions in brain oscillations in the gamma band (γ, >30 Hz). Noninvasive gamma entrainment using sensory stimulation (GENUS) through auditory and visual sensory stimulation at 40 Hz reduces AD pathology, such as amyloid and tau levels; prevents cerebral atrophy; and improves behavioral testing performance in mouse models of AD. Mechanistically, this might occur through calcium-mediated activation of myelin and synaptic genes [82].

Therefore, GENUS is among the most promising approaches for AD treatment [83]. A phase 1 feasibility study (NCT04042922, ClinicalTrials.gov) was conducted in cognitively normal volunteers ($n = 25$), patients with mild AD dementia ($n = 16$), and patients with epilepsy who underwent intracranial electrode monitoring ($n = 2$) to assess the safety and feasibility of a single brief GENUS session to induce entrainment. The phase 1 study showed that 40 Hz GENUS was safe and effectively induced entrainment in both cortical regions and in other cortical and subcortical structures, such as the hippocampus, amygdala, insula, and gyrus rectus.

The next study was a single-blinded, randomized, placebo-controlled phase 2A pilot study (NCT04055376) in patients with mild probable AD dementia ($n = 15$) to assess safety, compliance, entrainment, and exploratory clinical outcomes after chronic daily 40-Hz sensory stimulation for 3 months. The study demonstrated that chronic daily 40-Hz light and sound GENUS was well tolerated, and that compliance was equally high in both the control and active groups, with participants equally inaccurate in guessing their group assignments prior to unblinding. Electroencephalography recordings show that our 40-Hz GENUS device safely and effectively induced 40-Hz entrainment in participants with mild AD dementia. After 3 months of daily stimulation, the group receiving 40-Hz stimulation showed less ventricular dilation and hippocampal atrophy and better performance on the face-name association delayed recall test. These results support further evaluation of GENUS in a pivotal clinical trial to evaluate its potential as a novel disease-modifying therapeutic for patients with AD [26].

## INVASIVE TECHNIQUES

*Deep brain stimulation*

Deep brain stimulation (DBS) has been used to treat several movement disorders and psychiatric disorders, and it has been used as an experimental

treatment for obesity, anorexia, chronic pain, and AD [84]. DBS requires trepanation for the surgical placement of wire leads and electrodes to stimulate targeted deep brain structures. The electrical fields can then be adjusted by trained experts throughout the treatment course of the patient. Electricity is supplied by a battery-driven power supply that is placed subcutaneously near the collarbone. In patients with AD, DBS is thought to work through neuromodulation of memory circuits by directly stimulating deep brain structures involved in memory formation and recall [28]. Previous studies have shown a strong correlation between cognitive decline in patients with AD and decreased cerebral glucose metabolism in their brain cortices [85, 86]. Pilot clinical trials on AD patients have been conducted to stimulate the nucleus basalis of Meynert [30], the fornix [27–29, 31, 32, 34], and the hypothalamus [27]. These studies have reported the reversal of impaired glucose utilization [27–29, 31] and a slower cognitive decline [27–30]. However, other studies using DBS showed no improvement in the cognitive function of patients or had at least some patients who showed no improvement. Altogether, these studies suggest that DBS may be more beneficial in patients more than 65 years old [30, 31, 34].

Serious adverse effects have been reported, including infection, the need for electrode repositioning, chronic subdural hematoma, syncope, seizures, altered mental status, rigidity, and agitation [32–34]. On the other hand, several studies have reported no serious or permanent adverse effects [27, 30, 31]. In the multicenter ADvance Trial, only 5 of 42 patients experienced serious adverse events, including infection, the need for electrode repositioning, and chronic subdural hematoma [32, 34]. In addition, there are several ethical considerations of DBS treatment that are currently being discussed regarding psychiatric and cognitive adverse effects, and about obtaining objective informed consent [84, 87, 88]. More studies are needed to determine the efficacy of DBS for treating patients with AD. The optimal stimulation parameters for treating patients with AD must also be determined.

*Vagus nerve stimulation*

Vagus nerve stimulation (VNS) involves a surgery in which a unidirectional wire is wrapped around the vagus nerve in the cervical area and connected to a battery-powered device implanted subcutaneously in the anterior chest wall [43, 89]. The device emits intermittent electrical currents through the vagus nerve projecting to the locus coeruleus, a brain nucleus rich in noradrenergic neurons. Consequently, it is anticipated that VNS may stimulate noradrenergic afferences to modulate synaptic plasticity in the hippocampus and other memory-related brain regions [90]. Stimulation of the vagus nerve has been shown to improve cognition [91] and memory [90] and cause changes in neuronal activity in deep brain structures such as the thalamus, hippocampus, and amygdala [92, 93]. The effect of VNS is commonly assessed via functional magnetic resonance imaging as it can immediately show increased blood flow to regions activated during VNS [94]. Pilot studies of VNS on AD patients have shown improvements in memory or no significant decline after 3 months or 1 year of treatment [35, 36]. They also found VNS to be well tolerated by patients.

## DISCUSSION

There is growing interest in seeking nonpharmacological solutions for AD. Many devices in development are noninvasive, which adds an element of safety. Surveillance can also be easier with a device than with pharmacological treatment if the device needs to be applied. The downside of such treatment is that many devices require frequent visits to the clinic. They can be expensive to acquire, and the cost of treatment might not be reimbursed by insurance companies. Because some devices require frequent visits to the hospital, there might be an added burden on caregivers.

Ideally, the future of AD therapeutics will be combination therapy. None of the noninvasive devices would exclude the use of anti-amyloid monoclonal antibodies, which can be deployed simultaneously in practice. However, device-based therapies might complicate research by confounding the interpretation of clinical benefit.

An unresolved question is whether device-based therapies are symptomatic or disease-modifying. There is little autopsy data available with which to assess whether pathology was altered, and biomarker evidence is not widely available. Therefore, it is likely that the clinical implication is that most efficacy from these devices is symptomatic.

Priorities for the deployment of device-based nonpharmacological treatment of AD should be subdivided into research outlooks and clinical implications. Among the latter, a further subgrouping

may be important to distinguish immediate clinical implications from typical geriatric multidimensional implications, such as effects on gait instability and cognitive impairment.

## CONCLUSION

Many devices are in development for the treatment of AD. Treatments using devices have potential advantages over other therapeutic intervention modalities, including a time-limited window of treatment exposure, signs of efficacy that may be detected more quickly, and motivated patients, improving adherence to treatment. Power calculations and regulatory pathways indicate that the clinical trial sample sizes necessary to be considered approvable are often in the hundreds rather than the thousands. Many devices are reasonably well tolerated. Some are repurposed from treatments for other neurological conditions. The disadvantages of device-related treatments include frequency of treatment, potential invasiveness, and cost. Priorities for the nonpharmacological treatment of AD should be subdivided into research outlooks and clinical implications. Research outlooks provide a context for further development of a device based on a mechanism of action without a specific path to commercialization and approval. Clinical implications center on the likelihood of seeing devices introduced into clinical practice. Among the latter, a further subgrouping is necessary to distinguish immediate clinical implications from typical geriatric multidimensional ones, in particular the effects on gait instability and cognitive impairment. Many devices could be seen as potentially having subacute effects on cognition but could also have effects on other aspects of the neuroaxis, such as gait and mobility (e.g., DBS). Part of the determination of clinical effect is the localization of where the technology is applied. Clinical implications also need to be considered in the context of how devices would be used in clinical settings. Would they be considered as adjunct therapy to disease modifying therapies? There is the growing concept of the multi-targeted approach to AD treatments.

Although they show great promise, it is our opinion that more research is needed to determine the maximum length of therapeutic effects for these techniques, the optimal administration methods, and efficacy compared to neuropharmacological agents (including how the effects may be modulated by pharmaceuticals), and the potential of combination treatment methods [95].

## ACKNOWLEDGMENTS

We thank the staff of Neuroscience Publications at Barrow Neurological Institute for assistance with manuscript preparation.

## FUNDING

Supported by National Institutes of Health grants R01AG059008, and R01AG073212, and P30 AG072980, and by the Barrow Neurological Foundation.

## CONFLICT OF INTEREST

Dr. Sleem has no conflicts of interest to report. Dr. DeCourt declares that he is a consultant for Seq Biomarque. Dr. Sabbagh discloses that he has ownership interest (stock or stock options) in NeuroTau, uMethod Health, Lighthouse Pharmaceuticals, and Athira; he consults for Alzheon, Biogen, Roche-Genentech, T3D, Novo Nordisk, Signant Health, Prothena, Eisai, Lilly, and KeifeRx. Dr. Sabbagh is an editorial board member of this journal but was not involved in the peer-review process of this article nor had access to any information regarding its peer-review.

## REFERENCES

[1] (2022) 2022 Alzheimer's disease facts and figures. *Alzheimers Dement* **18**, 700-789.
[2] (2021) 2021 Alzheimer's disease facts and figures. *Alzheimers Dement* **17**, 327-406.
[3] Cerejeira J, Lagarto L, Mukaetova-Ladinska EB (2012) Behavioral and psychological symptoms of dementia. *Front Neurol* **3**, 73.
[4] Cummings J, Lee G, Nahed P, Kambar M, Zhong K, Fonseca J, Taghva K (2022) Alzheimer's disease drug development pipeline: 2022. *Alzheimers Dement (N Y)* **8**, e12295.
[5] Cotelli M, Calabria M, Manenti R, Rosini S, Zanetti O, Cappa SF, Miniussi C (2011) Improved language performance in Alzheimer disease following brain stimulation. *J Neurol Neurosurg Psychiatry* **82**, 794-797.
[6] Ahmed MA, Darwish ES, Khedr EM, El Serogy YM, Ali AM (2012) Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. *J Neurol* **259**, 83-92.
[7] Rabey JM, Dobronevsky E, Aichenbaum S, Gonen O, Marton RG, Khaigrekht M (2013) Repetitive transcranial magnetic stimulation combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's

disease: A randomized, double-blind study. *J Neural Transm (Vienna)* **120**, 813-819.

[8] Wu Y, Xu W, Liu X, Xu Q, Tang L, Wu S (2015) Adjunctive treatment with high frequency repetitive transcranial magnetic stimulation for the behavioral and psychological symptoms of patients with Alzheimer's disease: A randomized, double-blind, sham-controlled study. *Shanghai Arch Psychiatry* **27**, 280-288.

[9] Lee J, Choi BH, Oh E, Sohn EH, Lee AY (2016) Treatment of Alzheimer's disease with repetitive transcranial magnetic stimulation combined with cognitive training: A prospective, randomized, double-blind, placebo-controlled study. *J Clin Neurol* **12**, 57-64.

[10] Nguyen JP, Suarez A, Kemoun G, Meignier M, Le Saout E, Damier P, Nizard J, Lefaucheur JP (2017) Repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease. *Neurophysiol Clin* **47**, 47-53.

[11] Sabbagh M, Sadowsky C, Tousi B, Agronin ME, Alva G, Armon C, Bernick C, Keegan AP, Karantzoulis S, Baror E, Ploznik M, Pascual-Leone A (2020) Effects of a combined transcranial magnetic stimulation (TMS) and cognitive training intervention in patients with Alzheimer's disease. *Alzheimers Dement* **16**, 641-650.

[12] Boggio PS, Khoury LP, Martins DC, Martins OE, de Macedo EC, Fregni F (2009) Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease. *J Neurol Neurosurg Psychiatry* **80**, 444-447.

[13] Bystad M, Rasmussen ID, Gronli O, Aslaksen PM (2017) Can 8 months of daily tDCS application slow the cognitive decline in Alzheimer's disease? A case study. *Neurocase* **23**, 146-148.

[14] Im JJ, Jeong H, Bikson M, Woods AJ, Unal G, Oh JK, Na S, Park JS, Knotkova H, Song IU, Chung YA (2019) Effects of 6-month at-home transcranial direct current stimulation on cognition and cerebral glucose metabolism in Alzheimer's disease. *Brain Stimul* **12**, 1222-1228.

[15] Khedr EM, Salama RH, Abdel Hameed M, Abo Elfetoh N, Seif P (2019) Therapeutic role of transcranial direct current stimulation in Alzheimer disease patients: Double-blind, placebo-controlled clinical trial. *Neurorehabil Neural Repair* **33**, 384-394.

[16] Smirni D, Oliveri M, Misuraca E, Catania A, Vernuccio L, Picciolo V, Inzerillo F, Barbagallo M, Cipolotti L, Turriziani P (2021) Verbal fluency in mild Alzheimer's disease: Transcranial direct current stimulation over the dorsolateral prefrontal cortex. *J Alzheimers Dis* **81**, 1273-1283.

[17] Bréchet L, Yu W, Biagi MC, Ruffini G, Gagnon M, Manor B, Pascual-Leone A (2021) Patient-tailored, home-based non-invasive brain stimulation for memory deficits in dementia due to Alzheimer's disease. *Front Neurol* **12**, 598135.

[18] Sprugnoli G, Munsch F, Cappon D, Paciorek R, Macone J, Connor A, El Fakhri G, Salvador R, Ruffini G, Donohoe K, Shafi MM, Press D, Alsop DC, Pascual Leone A, Santarnecchi E (2021) Impact of multisession 40 Hz tACS on hippocampal perfusion in patients with Alzheimer's disease. *Alzheimers Res Ther* **13**, 203.

[19] Benussi A, Cantoni V, Grassi M, Brechet L, Michel CM, Datta A, Thomas C, Gazzina S, Cotelli MS, Bianchi M, Premi E, Gadola Y, Cotelli M, Pengo M, Perrone F, Scolaro M, Archetti S, Solje E, Padovani A, Pascual-Leone A, Borroni B (2022) Increasing brain gamma activity improves episodic memory and restores cholinergic dysfunction in Alzheimer's disease. *Ann Neurol* **92**, 322-334.

[20] Saltmarche AE, Naeser MA, Ho KF, Hamblin MR, Lim L (2017) Significant improvement in cognition in mild to moderately severe dementia cases treated with transcranial plus intranasal photobiomodulation: Case series report. *Photomed Laser Surg* **35**, 432-441.

[21] Nagy EN, Ali AY, Behiry ME, Naguib MM, Elsayed MM (2021) Impact of combined photo-biomodulation and aerobic exercise on cognitive function and quality-of-life in elderly Alzheimer patients with anemia: A randomized clinical trial. *Int J Gen Med* **14**, 141-152.

[22] Beisteiner R, Matt E, Fan C, Baldysiak H, Schonfeld M, Philippi Novak T, Amini A, Aslan T, Reinecke R, Lehrner J, Weber A, Reime U, Goldenstedt C, Marlinghaus E, Hallett M, Lohse-Busch H (2020) Transcranial pulse stimulation with ultrasound in Alzheimer's disease-a new navigated focal brain therapy. *Adv Sci (Weinh)* **7**, 1902583.

[23] University Hospital, Tours (2020) Effects of auditory brain stimulation by "pink noise" on memory capacities in Alzheimer's disease: Proof of concept study. https://clinicaltrials.gov/ct2/show/NCT04570761

[24] Arendash G, Cao C, Abulaban H, Baranowski R, Wisniewski G, Becerra L, Andel R, Lin X, Zhang X, Wittwer D, Moulton J, Arrington J, Smith A (2019) A clinical trial of transcranial electromagnetic treatment in Alzheimer's disease: Cognitive enhancement and associated changes in cerebrospinal fluid, blood, and brain imaging. *J Alzheimers Dis* **71**, 57-82.

[25] Arendash G, Abulaban H, Steen S, Andel R, Wang Y, Bai Y, Baranowski R, McGarity J, Scritsmier L, Lin X, Shen N, Aljassabi A, Li Y, Cao C (2022) Transcranial electromagnetic treatment stops Alzheimer's disease cognitive decline over a 2(1/2)-year period: A pilot study. *Medicines (Basel)* **9**, 42.

[26] Chan D, Suk HJ, Jackson BL, Milman NP, Stark D, Klerman EB, Kitchener E, Fernandez Avalos VS, de Weck G, Banerjee A, Beach SD, Blanchard J, Stearns C, Boes AD, Uitermarkt B, Gander P, Howard M, 3rd, Sternberg EJ, Nieto-Castanon A, Anteraper S, Whitfield-Gabrieli S, Brown EN, Boyden ES, Dickerson BC, Tsai LH (2022) Gamma frequency sensory stimulation in mild probable Alzheimer's dementia patients: Results of feasibility and pilot studies. *PLoS One* **17**, e0278412.

[27] Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, Wherrett J, Naglie G, Hamani C, Smith GS, Lozano AM (2010) A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. *Ann Neurol* **68**, 521-534.

[28] Smith GS, Laxton AW, Tang-Wai DF, McAndrews MP, Diaconescu AO, Workman CI, Lozano AM (2012) Increased cerebral metabolism after 1 year of deep brain stimulation in Alzheimer disease. *Arch Neurol* **69**, 1141-1148.

[29] Fontaine D, Deudon A, Lemaire JJ, Razzouk M, Viau P, Darcourt J, Robert P (2013) Symptomatic treatment of memory decline in Alzheimer's disease by deep brain stimulation: A feasibility study. *J Alzheimers Dis* **34**, 315-323.

[30] Kuhn J, Hardenacke K, Lenartz D, Gruendler T, Ullsperger M, Bartsch C, Mai JK, Zilles K, Bauer A, Matusch A, Schulz RJ, Noreik M, Buhrle CP, Maintz D, Woopen C, Haussermann P, Hellmich M, Klosterkotter J, Wiltfang J, Maarouf M, Freund HJ, Sturm V (2015) Deep brain stimulation of the nucleus basalis of Meynert in Alzheimer's dementia. *Mol Psychiatry* **20**, 353-360.

[31] Lozano AM, Fosdick L, Chakravarty MM, Leoutsakos JM, Munro C, Oh E, Drake KE, Lyman CH, Rosenberg PB,

Anderson WS, Tang-Wai DF, Pendergrass JC, Salloway S, Asaad WF, Ponce FA, Burke A, Sabbagh M, Wolk DA, Baltuch G, Okun MS, Foote KD, McAndrews MP, Giacobbe P, Targum SD, Lyketsos CG, Smith GS (2016) A phase II study of fornix deep brain stimulation in mild Alzheimer's disease. *J Alzheimers Dis* **54**, 777-787.

[32] Ponce FA, Asaad WF, Foote KD, Anderson WS, Rees Cosgrove G, Baltuch GH, Beasley K, Reymers DE, Oh ES, Targum SD, Smith GS, Lyketsos CG, Lozano AM, ADvance Research Group (2016) Bilateral deep brain stimulation of the fornix for Alzheimer's disease: Surgical safety in the ADvance trial. *J Neurosurg* **125**, 75-84.

[33] McMullen DP, Rosenberg P, Cheng J, Smith GS, Lyketsos C, Anderson WS (2016) Bilateral cortical encephalomalacia in a patient implanted with bilateral deep brain stimulation for Alzheimer's disease: A case report. *Alzheimer Dis Assoc Disord* **30**, 70-72.

[34] Leoutsakos JS, Yan H, Anderson WS, Asaad WF, Baltuch G, Burke A, Chakravarty MM, Drake KE, Foote KD, Fosdick L, Giacobbe P, Mari Z, McAndrews MP, Munro CA, Oh ES, Okun MS, Pendergrass JC, Ponce FA, Rosenberg PB, Sabbagh MN, Salloway S, Tang-Wai DF, Targum SD, Wolk D, Lozano AM, Smith GS, Lyketsos CG (2018) Deep brain stimulation targeting the fornix for mild Alzheimer dementia (the ADvance Trial): A two year follow-up including results of delayed activation. *J Alzheimers Dis* **64**, 597-606.

[35] Sjögren MJ, Hellstrom PT, Jonsson MA, Runnerstam M, Silander HC, Ben-Menachem E (2002) Cognition-enhancing effect of vagus nerve stimulation in patients with Alzheimer's disease: A pilot study. *J Clin Psychiatry* **63**, 972-980.

[36] Merrill CA, Jonsson MA, Minthon L, Ejnell H, H CsS, Blennow K, Karlsson M, Nordlund A, Rolstad S, Warkentin S, Ben-Menachem E, Sjogren MJ (2006) Vagus nerve stimulation in patients with Alzheimer's disease: Additional follow-up results of a pilot study through 1 year. *J Clin Psychiatry* **67**, 1171-1178.

[37] Barker AT, Jalinous R, Freeston IL (1985) Non-invasive magnetic stimulation of human motor cortex. *Lancet* **1**, 1106-1107.

[38] Chou YH, You H, Wang H, Zhao YP, Hou B, Chen NK, Feng F (2015) Effect of repetitive transcranial magnetic stimulation on fMRI resting-state connectivity in multiple system atrophy. *Brain Connect* **5**, 451-459.

[39] Ridding MC, Ziemann U (2010) Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. *J Physiol* **588**, 2291-2304.

[40] Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, Lu B (2010) Direct current stimulation promotes BDNF-dependent synaptic plasticity: Potential implications for motor learning. *Neuron* **66**, 198-204.

[41] Di Lazzaro V, Oliviero A, Pilato F, Saturno E, Dileone M, Marra C, Daniele A, Ghirlanda S, Gainotti G, Tonali PA (2004) Motor cortex hyperexcitability to transcranial magnetic stimulation in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **75**, 555-559.

[42] Ferreri F, Vecchio F, Vollero L, Guerra A, Petrichella S, Ponzo D, Maatta S, Mervaala E, Kononen M, Ursini F, Pasqualetti P, Iannello G, Rossini PM, Di Lazzaro V (2016) Sensorimotor cortex excitability and connectivity in Alzheimer's disease: A TMS-EEG co-registration study. *Hum Brain Mapp* **37**, 2083-2096.

[43] George MS, Aston-Jones G (2010) Noninvasive techniques for probing neurocircuitry and treating illness: Vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology* **35**, 301-316.

[44] Lloyd JO, Chisholm KI, Oehle B, Jones MG, Okine BN, Al-Kaisy A, Lambru G, McMahon SB, Andreou AP (2020) Cortical mechanisms of single-pulse transcranial magnetic stimulation in migraine. *Neurotherapeutics* **17**, 1973-1987.

[45] Chou YH, Hickey PT, Sundman M, Song AW, Chen NK (2015) Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson disease: A systematic review and meta-analysis. *JAMA Neurol* **72**, 432-440.

[46] Chou YH, Ton That V, Sundman M (2020) A systematic review and meta-analysis of rTMS effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* **86**, 1-10.

[47] Hummel FC, Cohen LG (2006) Non-invasive brain stimulation: A new strategy to improve neurorehabilitation after stroke? *Lancet Neurol* **5**, 708-712.

[48] O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, McDonald WM, Avery D, Fitzgerald PB, Loo C, Demitrack MA, George MS, Sackeim HA (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: A multisite randomized controlled trial. *Biol Psychiatry* **62**, 1208-1216.

[49] Ma J, Wang J, Lv C, Pang J, Han B, Wang M, Gen Y (2017) The role of hippocampal structural synaptic plasticity in repetitive transcranial magnetic stimulation to improve cognitive function in male SAMP8 mice. *Cell Physiol Biochem* **41**, 137-144.

[50] Huang Z, Tan T, Du Y, Chen L, Fu M, Yu Y, Zhang L, Song W, Dong Z (2017) Low-frequency repetitive transcranial magnetic stimulation ameliorates cognitive function and synaptic plasticity in APP23/PS45 mouse model of Alzheimer's disease. *Front Aging Neurosci* **9**, 292.

[51] Dong X, Yan L, Huang L, Guan X, Dong C, Tao H, Wang T, Qin X, Wan Q (2018) Repetitive transcranial magnetic stimulation for the treatment of Alzheimer's disease: A systematic review and meta-analysis of randomized controlled trials. *PLoS One* **13**, e0205704.

[52] Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMSCG (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* **120**, 2008-2039.

[53] Reis J, John D, Heimeroth A, Mueller HH, Oertel WH, Arndt T, Rosenow F (2006) Modulation of human motor cortex excitability by single doses of amantadine. *Neuropsychopharmacology* **31**, 2758-2766.

[54] Nitsche MA, Paulus W (2001) Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology* **57**, 1899-1901.

[55] Nitsche MA, Jaussi W, Liebetanz D, Lang N, Tergau F, Paulus W (2004) Consolidation of human motor cortical neuroplasticity by D-cycloserine. *Neuropsychopharmacology* **29**, 1573-1578.

[56] Cai M, Guo Z, Xing G, Peng H, Zhou L, Chen H, McClure MA, He L, Xiong L, He B, Du F, Mu Q (2019) Transcranial direct current stimulation improves cognitive function in mild to moderate Alzheimer disease: A meta-analysis. *Alzheimer Dis Assoc Disord* **33**, 170-178.

[57] Chu CS, Li CT, Brunoni AR, Yang FC, Tseng PT, Tu YK, Stubbs B, Carvalho AF, Thompson T, Rajji TK, Yeh TC, Tsai CK, Chen TY, Li DJ, Hsu CW, Wu YC, Yu CL, Liang CS (2021) Cognitive effects and acceptability of non-invasive brain stimulation on Alzheimer's disease and mild

cognitive impairment: A component network meta-analysis. *J Neurol Neurosurg Psychiatry* **92**, 195-203.

[58] Frohlich F, McCormick DA (2010) Endogenous electric fields may guide neocortical network activity. *Neuron* **67**, 129-143.

[59] Jeong WH, Kim WI, Lee JW, Park HK, Song MK, Choi IS, Han JY (2021) Modulation of long-term potentiation by gamma frequency transcranial alternating current stimulation in transgenic mouse models of Alzheimer's disease. *Brain Sci* **11**, 1532.

[60] Veniero D, Vossen A, Gross J, Thut G (2015) Lasting EEG/MEG aftereffects of rhythmic transcranial brain stimulation: Level of control over oscillatory network activity. *Front Cell Neurosci* **9**, 477.

[61] Zomorrodi R, Loheswaran G, Pushparaj A, Lim L (2019) Pulsed near infrared transcranial and intranasal photobiomodulation significantly modulates neural oscillations: A pilot exploratory study. *Sci Rep* **9**, 6309.

[62] Chao LL (2019) Effects of home photobiomodulation treatments on cognitive and behavioral function, cerebral perfusion, and resting-state functional connectivity in patients with dementia: A pilot trial. *Photobiomodul Photomed Laser Surg* **37**, 133-141.

[63] Hamblin MR (2018) Photobiomodulation for traumatic brain injury and stroke. *J Neurosci Res* **96**, 731-743.

[64] Liebert A, Bicknell B, Laakso EL, Heller G, Jalilitabaei P, Tilley S, Mitrofanis J, Kiat H (2021) Improvements in clinical signs of Parkinson's disease using photobiomodulation: A prospective proof-of-concept study. *BMC Neurol* **21**, 256.

[65] Cardoso FDS, Lopes Martins RAB, Gomes da Silva S (2020) Therapeutic potential of photobiomodulation in Alzheimer's disease: A systematic review. *J Lasers Med Sci* **11**, S16-S22.

[66] De Taboada L, Yu J, El-Amouri S, Gattoni-Celli S, Richieri S, McCarthy T, Streeter J, Kindy MS (2011) Transcranial laser therapy attenuates amyloid-beta peptide neuropathology in amyloid-beta protein precursor transgenic mice. *J Alzheimers Dis* **23**, 521-535.

[67] da Luz Eltchechem C, Salgado ASI, Zangaro RA, da Silva Pereira MC, Kerppers, II, da Silva LA, Parreira RB (2017) Transcranial LED therapy on amyloid-beta toxin 25–35 in the hippocampal region of rats. *Lasers Med Sci* **32**, 749-756.

[68] Purushothuman S, Johnstone DM, Nandasena C, Mitrofanis J, Stone J (2014) Photobiomodulation with near infrared light mitigates Alzheimer's disease-related pathology in cerebral cortex – evidence from two transgenic mouse models. *Alzheimers Res Ther* **6**, 2.

[69] Cho GM, Lee SY, Park JH, Kim MJ, Park KJ, Choi BT, Shin YI, Kim NG, Shin HK (2020) Photobiomodulation using a low-level light-emitting diode improves cognitive dysfunction in the 5XFAD mouse model of Alzheimer's disease. *J Gerontol A Biol Sci Med Sci* **75**, 631-639.

[70] Lu Y, Wang R, Dong Y, Tucker D, Zhao N, Ahmed ME, Zhu L, Liu TC, Cohen RM, Zhang Q (2017) Low-level laser therapy for beta amyloid toxicity in rat hippocampus. *Neurobiol Aging* **49**, 165-182.

[71] Yang X, Askarova S, Sheng W, Chen JK, Sun AY, Sun GY, Yao G, Lee JC (2010) Low energy laser light (632.8nm) suppresses amyloid-beta peptide-induced oxidative and inflammatory responses in astrocytes. *Neuroscience* **171**, 859-868.

[72] Barrett DW, Gonzalez-Lima F (2013) Transcranial infrared laser stimulation produces beneficial cognitive and emotional effects in humans. *Neuroscience* **230**, 13-23.

[73] Darrow DP (2019) Focused ultrasound for neuromodulation. *Neurotherapeutics* **16**, 88-99.

[74] Legon W, Ai L, Bansal P, Mueller JK (2018) Neuromodulation with single-element transcranial focused ultrasound in human thalamus. *Hum Brain Mapp* **39**, 1995-2006.

[75] Krishna V, Sammartino F, Rezai A (2018) A review of the current therapies, challenges, and future directions of transcranial focused ultrasound technology: Advances in diagnosis and treatment. *JAMA Neurol* **75**, 246-254.

[76] Capezuti E, Pain K, Alamag E, Chen X, Philibert V, Krieger AC (2022) Systematic review: Auditory stimulation and sleep. *J Clin Sleep Med* **18**, 1697-1709.

[77] Papalambros NA, Santostasi G, Malkani RG, Braun R, Weintraub S, Paller KA, Zee PC (2017) Acoustic enhancement of sleep slow oscillations and concomitant memory improvement in older adults. *Front Hum Neurosci* **11**, 109.

[78] Papalambros NA, Weintraub S, Chen T, Grimaldi D, Santostasi G, Paller KA, Zee PC, Malkani RG (2019) Acoustic enhancement of sleep slow oscillations in mild cognitive impairment. *Ann Clin Transl Neurol* **6**, 1191-1201.

[79] Dragicevic N, Bradshaw PC, Mamcarz M, Lin X, Wang L, Cao C, Arendash GW (2011) Long-term electromagnetic field treatment enhances brain mitochondrial function of both Alzheimer's transgenic mice and normal mice: A mechanism for electromagnetic field-induced cognitive benefit? *Neuroscience* **185**, 135-149.

[80] Perez FP, Bandeira JP, Perez Chumbiauca CN, Lahiri DK, Morisaki J, Rizkalla M (2022) Multidimensional insights into the repeated electromagnetic field stimulation and biosystems interaction in aging and age-related diseases. *J Biomed Sci* **29**, 39.

[81] Perez FP, Maloney B, Chopra N, Morisaki JJ, Lahiri DK (2021) Repeated electromagnetic field stimulation lowers amyloid-beta peptide levels in primary human mixed brain tissue cultures. *Sci Rep* **11**, 621.

[82] Adaikkan C, Middleton SJ, Marco A, Pao PC, Mathys H, Kim DN, Gao F, Young JZ, Suk HJ, Boyden ES, McHugh TJ, Tsai LH (2019) Gamma entrainment binds higher-order brain regions and offers neuroprotection. *Neuron* **102**, 929-943 e928.

[83] Manippa V, Palmisano A, Filardi M, Vilella D, Nitsche MA, Rivolta D, Logroscino G (2022) An update on the use of gamma (multi)sensory stimulation for Alzheimer's disease treatment. *Front Aging Neurosci* **14**, 1095081.

[84] Ovadia D, Bottini G (2015) Neuroethical implications of deep brain stimulation in degenerative disorders. *Curr Opin Neurol* **28**, 598-603.

[85] Alexander GE, Chen K, Pietrini P, Rapoport SI, Reiman EM (2002) Longitudinal PET evaluation of cerebral metabolic decline in dementia: A potential outcome measure in Alzheimer's disease treatment studies. *Am J Psychiatry* **159**, 738-745.

[86] Smith GS, de Leon MJ, George AE, Kluger A, Volkow ND, McRae T, Golomb J, Ferris SH, Reisberg B, Ciaravino J, et al. (1992) Topography of cross-sectional and longitudinal glucose metabolic deficits in Alzheimer's disease. Pathophysiologic implications. *Arch Neurol* **49**, 1142-1150.

[87] Viana JNM, Gilbert F (2019) Deep brain stimulation for people with Alzheimer's disease: Anticipating potential effects on the tripartite self. *Dementia (London)* **18**, 2836-2855.

[88] Gilbert F (2014) Self-estrangement & deep brain stimulation: Ethical issues related to forced explantation. *Neuroethics* **8**, 107-114.

[89] George MS, Sackeim HA, Rush AJ, Marangell LB, Nahas Z, Husain MM, Lisanby S, Burt T, Goldman J, Ballenger

JC (2000) Vagus nerve stimulation: A new tool for brain research and therapy. *Biol Psychiatry* **47**, 287-295.

[90] Zuo Y, Smith DC, Jensen RA (2007) Vagus nerve stimulation potentiates hippocampal LTP in freely-moving rats. *Physiol Behav* **90**, 583-589.

[91] Boon P, Moors I, De Herdt V, Vonck K (2006) Vagus nerve stimulation and cognition. *Seizure* **15**, 259-263.

[92] Henry TR, Bakay RA, Votaw JR, Pennell PB, Epstein CM, Faber TL, Grafton ST, Hoffman JM (1998) Brain blood flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: I. Acute effects at high and low levels of stimulation. *Epilepsia* **39**, 983-990.

[93] Broncel A, Bocian R, Klos-Wojtczak P, Kulbat-Warycha K, Konopacki J (2020) Vagal nerve stimulation as a promising tool in the improvement of cognitive disorders. *Brain Res Bull* **155**, 37-47.

[94] Sucholeiki R, Alsaadi TM, Morris GL, 3rd, Ulmer JL, Biswal B, Mueller WM (2002) fMRI in patients implanted with a vagal nerve stimulator. *Seizure* **11**, 157-162.

[95] Al Qasem W, Abubaker M, Kvasnak E (2022) Working memory and transcranial-alternating current stimulation-state of the art: Findings, missing, and challenges. *Front Psychol* **13**, 822545.