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Review Article

Application of transcranial brain stimulation in dementia

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Abstract

The number of patients with dementia grows rapidly as the global population ages, which posits tremendous health-care burden to the society. Only cholinesterase inhibitors and a N-methyl-D-aspartate receptor antagonist have been approved for treating patients with Alzheimer's disease (AD), and their clinical effects remained limited. Medical devices serve as an alternative therapeutic approach to modulating neural activities and enhancing cognitive function. Four major brain stimulation technologies including deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcranial ultrasound stimulation (TUS) have been applied to AD in a clinical trial setting. DBS allows electrical stimulation at the specified nucleus but remains resource-demanding, and after all, an invasive surgery; whereas TMS and tDCS are widely available and affordable but less ideal with respect to localization. The unique physical property of TUS, on the other hand, allows both thermal and mechanical energy to be transduced and focused for neuromodulation. In the context of dementia, using focused ultrasound to induce blood-brain barrier opening for delivering drugs and metabolizing amyloid protein has drawn great attention in recent years. Furthermore, low-intensity pulsed ultrasound has demonstrated its neuroprotective effects in both *in vitro* and *in vivo* studies, leading to ongoing clinical trials for AD. The potential and limitation of transcranial brain stimulation for treating patients with dementia would be discussed in this review.

Keywords: *Alzheimer's disease, Brain stimulation, Dementia, Focused ultrasound, Transcranial ultrasound*

Introduction

More than 55 million people have dementia worldwide currently and dementia has become a major health burden as the global population age. Dementia is a clinical syndrome characterized by progressive cognitive decline in memory and other domains, eventually leading to functional impairment in daily activities. Dementia is heterogeneous in terms of its etiology. Although Alzheimer's disease (AD) is considered the major cause of dementia, more than 30% of all dementia cases are of different types, such as lewy body dementia, vascular dementia (VaD), frontotemporal dementia, and several atypical Parkinsonian syndromes affecting both cognitive and motor systems of the brain. In fact, it is rare to see dementia of single pathology in older adults at the age of 80 years and above. Most older adults with dementia have underlying mixed type pathologies, with the most common combination of AD and vascular insults or Lewy bodies.

The clinical challenge comes from not only the complexity of dementia diagnosis but also the lack of effective treatment for cognitive impairment. During the past three decades, only four drugs including three types of cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and 1 N-methyl-D-aspartate receptor antagonist (memantine) gain approval by the US Food and Drug Administration (FDA) for treating AD. The overall effect of cholinesterase inhibitors, for example, is to maintain cognitive function for an average of 2 years, but they have never been demonstrated to halt the relentless disease course of cognitive deterioration. Earlier this year in 2023, FDA grants accelerated approval of lecanemab, an anti-amyloid antibody for AD treatment, but how the new drug may slow the progression of AD or improve cognitive function remains to be observed in the coming years.

Nonpharmacological management for patients with dementia has been diversely developed; music therapy, reminiscence therapy, aromatherapy, animal-assisted therapy, light therapy, cognitive stimulation therapy, to name a few.

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However, some of them may be shown to reduce agitation or have immediate symptomatic relief for anxiety but overall there is no good evidence of benefit for cognitive function. These nonpharmacological approaches may serve as adjunctive therapy in dementia care but none of them are proven to be effective treatment for dementia [1].

Most known risk factors of AD or dementia in general are concerned with vascular risks such as diabetes mellitus, midlife hypertension, smoking, and obesity. Other risks include head injury, *APOE4* allele and education attainment in early life. In other words, the strategies of dementia prevention are no different than the current approach of preventing heart disease; whereas both *APOE* gene and early life education are the factors not modifiable. We may continue to promote vascular health by lifestyle intervention, but there appears to be a lack of specific brain health intervention to prevent cognitive impairment or dementia.

In recent years, minimal invasive or noninvasive medical devices have been innovated and developed for brain health and some are of high potential for treating or preventing dementia. In this review, we would summarize the progress of several brain stimulation technologies applied in the clinical scenario of dementia, with particular emphasis on ultrasound neuromodulation [Table 1].

Electric and magnetic neuromodulation

Deep brain stimulation

Deep brain stimulation (DBS) is a neurosurgical approach to implant microelectrodes at specific targets in the brain, with these electrodes producing electrical impulses to regulate abnormal neural function. DBS has been well developed since early 1990s and is nowadays commonly employed to treat Parkinson's disease (PD), essential tremor (ET), dystonia, and epilepsy.

Human trials of DBS for AD started in 1984 with the target on the nucleus basalis of Meynert as this nucleus were considered the dominant source of cortical cholinergic innervation [2], but the trial did not show significant improvement in memory. It was not until 2010 that another paper on DBS in AD was published [3], where fornix was instead chosen to be the implantation target and some patients with mild AD did show cognitive improvement. Thereafter, a few case reports demonstrated feasibility or tolerability but none of them showed clinical benefits. A phase II randomized, double-blind trial of bilateral DBS at fornix showed that DBS for AD was safe and associated with increased cerebral glucose metabolism, but there were no differences in cognitive outcomes [4].

DBS remains a promising neuromodulation for AD and related dementia disorders. Future research may apply different sets of stimulation parameters and place electrodes at different targets to test the clinical effect. However, DBS is not only highly resource intensive but also considered invasive that it involves creating small holes in the skull to implant the electrodes and placing the device including the battery under the skin in the chest, making it less appealing to most older adults with cognitive impairment and multiple chronic diseases.

Table 1: Brain stimulation device in clinical application

Device	Physical effect	FDA indication	AD trial target
DBS	Electrical impulse	PD, ET, dystonia	NBM Fornix
TMS	Magnetic field	Depression	DLPFC
tDCS	Electrical impulse	None	DLPFC
TUS			
High-intensity FUS	Thermoablation	ET, PD tremor	None
Medium-intensity FUS	BBB opening	None	Frontal lobe
LIPUS	Mechanical force	None	Hippocampus

FDA: Food and drug administration, AD: Alzheimer's disease, DBS: Deep brain stimulation, PD: Parkinson's disease, ET: Essential tremor, NBM: Nucleus basalis of Meynert, TMS: Transcranial magnetic stimulation, DLPFC: Dorsolateral prefrontal cortex, tDCS: Transcranial direct current stimulation, TUS: Transcranial ultrasound stimulation, FUS: Focused ultrasound, BBB: Blood–brain barrier, LIPUS: Low-intensity-pulsed ultrasound stimulation

Transcranial magnetic stimulation

Noninvasive brain stimulation (NIBS) has generated considerable interest in the context of disease modifying or preventive strategies against dementia. Within the family of NIBS, transcranial magnetic stimulation (TMS) has received great attention for its safety, feasibility, affordability, and potential therapeutic efficacy in clinical application. TMS is a procedure that creates magnetic fields to stimulate nerve cells in the brain. Repetitive TMS (rTMS), delivered over a course of several weeks has been approved by the US FDA for treating refractory major depression in 2008. Cortical suppression or facilitation effects of rTMS can be controlled by setting the frequency to be low (<1 Hz) or high (>3 Hz) in the stimulation protocol. Most clinical trials of rTMS for AD (up to phase II) employed the high frequency protocol on dorsolateral prefrontal cortex and many showed cognitive benefits or at least stable maintenance in language and memory [5].

There are still several uncertain issues that need to be addressed. While the effect of rTMS on depression has been well established, many patients with AD have coexisting depression. The stimulation protocol in many trials is similar to that used for depression, and therefore, whether the benefit of rTMS in AD results from alleviating depressive symptoms is not clear. All these trials are of small sample size and it appears that the effects are robust only in those with mild AD. A larger group of AD participants, together with a matched control group, is preferred. The trial observation periods range from weeks to 6 months and the cognitive outcome measurement may be vulnerable to training effects, regression-to-the-mean effect, or data variation. Whether the benefits can be translated into a long term effect requires longitudinal studies in the future.

Transcranial electric stimulation

Transcranial direct current stimulation (tDCS) is an extensively investigated technique which delivers a low-intensity sustained electrical current to cortical neurons via scalp electrodes in an attempt to modulate brain excitability and

plasticity. Randomized controlled trials have been conducted in patients with AD and mild cognitive impairment (MCI), and anodal tDCS was usually applied with a current of 2 mA for 20–30 min per session and target region at the DLPFC. Most of the trial findings (up to phase II) showed short-term cognitive improvement in delayed recall memory, executive function, language, and global cognition [6]. Furthermore, higher dosing or multiple-session protocols may induce greater effects in terms of behavioral change than single-session protocols. Two clinical trials paired tDCS with cognitive training as a combined intervention for AD and MCI; however, their findings did not consistently show synergistic effects. Most of these tDCS trials are limited by their small sample size, and no previous study has ever examined the long term efficacy. Despite of its well-tolerated, safe, low-cost, and even wearable treatment modality, tDCS is not FDA approved yet. Since neuroplasticity is the supposed to be the main effect of tDCS, a combination approach with cognitive training over an extended period of time is recommended in future trials.

Transcranial ultrasound stimulation

Ultrasound has been widely applied in medical diagnostics. Focused ultrasound (FUS) is a rather novel modality that induces thermal and mechanical effects to a restricted brain region for clinical application via a transducer, lens or arrays. Furthermore, the advance of stereotactic techniques of FUS coupling with real-time magnetic resonance imaging allows precise localization of treatment target and monitoring of sonication effects. The principal interest of therapeutic application of FUS is that the neurobiological effects can be transmitted through the intact skull without surgical operation or craniectomy. FUS sonication transmits thermal and mechanical energy to the medium that it passes through, while how these effects are differentially delivered to the brain tissue depends upon a variety of ultrasound parameters, such as intensity, duty cycle, burst duration, inter-stimulus interval, or frequency.

High-intensity focused ultrasound

The FUS exposure can be further divided into 3 categories: high intensity, medium intensity, and low intensity [7]. High-intensity FUS (HIFU) as thermoablation has been FDA approved for treating various benign and malignant tumors such as prostate cancer. Unlike radiation therapy, it has no cumulative effect after repeated treatment. With the coupling of MR, a well-targeted lesion can be created when applying HIFU, and therefore transcranial HIFU has been used as a lesioning tool for thalamotomy or pallidotomy in various trials. MR-guided HIFU was approved by FDA for treating drug refractory ET in 2016, and then for Parkinsonian tremor 2 years later in 2018. In the context of AD or related dementia, however, there is little role for HIFU as a treatment modality since its main effect is lesioning or tissue destruction rather than regeneration or functional restoration.

Medium-intensity focused ultrasound

FUS in the pulse mode has lower average intensities and allows for cooling between pulses. The pulsed FUS has demonstrated mechanical effects to increase vascular permeability. Blood − brain barrier (BBB) has long been seen as a critical obstacle to delivering drugs, and therefore, the possibility of incorporating the medium-intensity pulsed FUS to achieve BBB opening is of great clinical interest. The use of pulsed FUS in combination with microbubbles can further increase BBB permeability while preserve the resilience of cerebral vessels without hemorrhagic or ischemic complications. In the context of treatment for dementia, a pilot study (phase I) of using transcranial medium-intensity FUS to sonicate a focal area of right frontal lobe in mild to moderate AD has been conducted and which showed the increased permeability to gadolinium and the recovery of BBB integrity within 24 h [8]. Another application (phase I) of medium-intensity FUS onto hippocampus in early AD also showed focal BBB opening, together with its safety and reproducibility [9]. These two trials suggest a great potential of FUS for drug delivery in treating AD and other neurodegenerative disorders in general; however, at the time of BBB opening for drug delivery, how to prevent neurotoxic metabolites from entering into the brain tissue is another safety concern awaits further investigation.

Low-intensity focused ultrasound

In addition to focal thermoablation and BBB opening, FUS in a lower intensity or low-intensity pulsed ultrasound (LIPUS) as a new modality of brain stimulation to modulate neural activities has raised renewed interest in recent years in terms of therapeutic intervention for dementia or other neurodegenerative disorders [Figure 1].

Low-intensity pulsed ultrasound *in vitro* studies

There is a growing body of evidence that LIPUS stimulation is mainly neuroprotective at the cellular level. In a PC12 cell culture study, LIPUS was shown to increase nerve growth factor (NGF)-induced neurite length, and the activation of underlying ERK1/2–CREB–Trx-1 pathway was likely attributed to its mechano-transduction [10]. Brain-derived neurotrophic factor (BDNF) is also a major regulator of synaptic plasticity and neuronal survival [11], and it has been shown in a population-based study that increased levels of BDNF were associated with lower risks of dementia [12]. LIPUS stimulation activates TrkB and Akt signaling and increases intracellular calcium levels, resulting in the elevation of BDNF protein levels in astrocytes [13]. Autophagy, or cellular self-digestion, is an essential process to eliminate abnormal protein aggregates, and the neuron-specific loss of autophagy can lead to neurodegeneration [14]. In the primary cultured neurons, LIPUS treatment increased the expression of LC3B, a marker for neuronal autophagy, consistent with the concept that mechanical waves may drive neuronal autophagy [15]. Moreover, LIPUS was found to modulate antioxidant proteins and protect neuronal cells via stretch-activated channels in a MPP+-induced neurotoxicity cell model [16]. All the above findings suggest that LIPUS stimulation as a modality of mechanotransduction may enhance nerve growth and neuroprotection through multiple pathways.

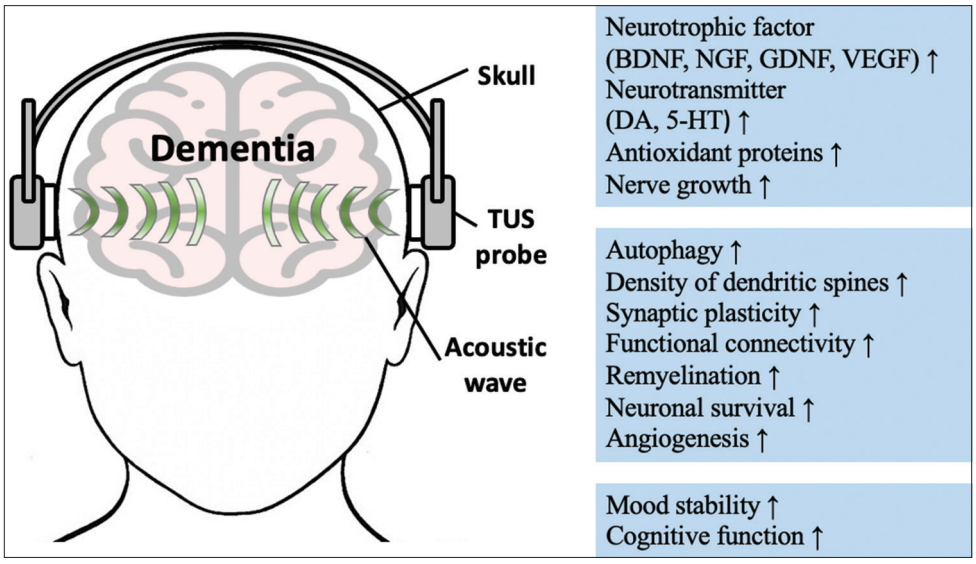

Figure 1: Neuroprotective effects of low-intensity pulsed transcranial ultrasound stimulation. TUS: Transcranial ultrasound stimulation, BDNF: Brain-derived neurotrophic factor, NGF: Nerve growth factor, GDNF: Glial cell line-derived neurotrophic factor, VEGF: Vascular endothelial growth factor, DA: Dopamine, 5-HT: Serotonin

Low-intensity pulsed ultrasound *in vivo* studies

In an AD rat model, LIPUS sonication leads to significantly increased protein expressions of NGF, BDNF, glial cell line-derived neurotrophic factor, and vascular endothelial growth factor in the stimulated hippocampi, suggesting its potential for maintaining neuronal survival in neurodegeneration [17-19]. Cerebral blood flow and neural activity are closely linked and coupled in the concept of neurovascular unit. In 2 mouse models of VaD and AD, LIPUS stimulation has also been demonstrated to upregulate endothelium-related genes as well as promote oligodendrocyte proliferation, suggesting that LIPUS has additional roles in angiogenesis and remyelination [20].

Although the progressive loss of neocortical and limbic cholinergic innervation, or the cholinergic hypothesis of AD, has driven the drug development and FDA approval of cholinesterase inhibitor for treating AD, other neurotransmitters including dopamine (DA) and serotonin (5-HT) have also gained attention for their role in AD [21], such that patients with AD were found to have lower levels of DA in many previous case-control studies [22]. Direct sonication of thalamus in a rat model showed an increase in the extracellular levels of DA and 5-HT, and the effect did not appear to be transient [23]; therefore, the sonication parameters are of critical importance in terms of optimizing the beneficial effect of LIPUS.

At the cellular or synaptic level, LIPUS stimulation can significantly increase the density of dendritic spines and enhance synaptic plasticity [24,25]. Furthermore, over a course of 2 years targeting at caudate and putamen in a Macaca mulatta primate model, LIPUS enhanced the resting state functional connectivity to the superior temporal cortex and insular cortex [26]. In this particular non-human primate study, it was demonstrated that long term safety of using LIPUS stimulation was achieved and the physiological effects was both regional and remote to the extent that the cortical or subcortical neurons were functionally connected.

The key aspect of LIPUS stimulation is to determine its clinical benefit on cognitive function if the ultimate goal of LIPUS is to apply to patients with dementia. In aforementioned *in vivo* studies, LIPUS treatment significantly improved learning and memory function in mice and rat models of AD and VaD [18-20]. Interestingly, pre-treatment of LIPUS could protect the brain against the neurotoxicity of aluminum chloride toxicity in a rat model [27], suggesting that the clinical benefit of LIPUS may be long-lasting for a period of time. The short-and long-term outcome of LIPUS stimulation may have to do with sonication parameters, treatment protocols and the choice of target region. Future investigation to optimize the effect of LIPUS to improve cognitive outcome for dementia is warranted.

Low-intensity pulsed ultrasound clinical studies

Before starting trials for the rather vulnerable group of patients with dementia, the safety issue of LIPUS is of great concern. Given that HIFU, the continuous and high intensity ultrasound with thermoablation effect, has been approved by FDA to treat patients with ET, and no severe complication was reported to date yet, LIPUS is of 10^{-3} lower order of intensity and thus presumably safe. In a phase I, double-blind, crossover study for patients with chronic pain, low-intensity transcranial ultrasound was applied and the results showed not only a great safety profile but also improvement in subjective mood following stimulation [28]. A systemic review of human studies of transcranial ultrasound neuromodulation up to the year of 2022 included a total of 35 studies or 677 participants from diverse cohorts, and which showed that no severe adverse effects were reported and mild symptoms such as headache, scalp heating, pruritis were observed only in 3.4% of all subjects [29].

LIPUS stimulation for dementia remains mostly in laboratory using animal models and only few clinical trials

exist [30-33]. Beisteiner *et al*. enrolled 35 patients with probable AD and employed transcranial pulse stimulation for 2 weeks. The preclinical results showed large safety margins and dose-dependent neuromodulation effects, with up to 3 months of cognitive improvement (phase I) [30]. A follow-up study by Popescu *et al*. further found that cognitive improvement correlated well with cortical thickness increase in AD-critical brain areas, suggesting that transcranial pulse stimulation may induce both functional and structural changes by only several weeks of treatment (phase I) [31]. Jeong *et al*. enrolled four patients with probable AD and employed low-intensity transcranial ultrasound with microbubble injected intravenously. They demonstrated mild improvement in memory, executive, and global cognitive function following hippocampal sonication. There was no evidence of BBB disruption after sonication, indicating that LIPUS could modulate regional neural activities and bring cognitive benefits without BBB opening (phase I) [32]. Shimokawa *et al*. conducted a randomized controlled trial of LIPUS for 22 patients with mild AD. Their protocol of LIPUS therapy was whole-brain stimulation through bilateral temporal bones for 1 h and three times per week as one session. After a total of six sessions with a 3-month interval between each one, the changes in AD assessment scale scores from baseline worsened gradually in the placebo group but remained stationary in the LIPUS group. Although the treatment effect did not reach statistical significance, the study demonstrated again the safety of using LIPUS stimulation in AD (phase II) [33].

Conclusion

Medical treatment for AD or dementia disorders in general remains much limited, and the development of innovative medical devices for brain stimulation brings new hope for patients with dementia. DBS, TMS and tDCS have been employed to successfully treat a variety of neurological disorders such as PD, ET and depression but never gained substantial progress in treating dementia. Transcranial ultrasound stimulation or FUS with different levels of sonication intensity is being actively developed. BBB opening with anti-AD drug delivery to the specified brain region is an area of enthusiastic research. With a growing body of supportive evidence from cell or animal studies, LIPUS or low-intensity ultrasound neuromodulation shows great promise in neuroprotection and provides a novel approach to treating AD and other dementia disorders. Future investigation may center on sonication parameter optimization, target region selection and treatment protocol development with the aim of improving cognitive outcome for dementia.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

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