

Neuromodulation in Alzheimer's Disease in the Therapy Process

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Abstract. Increasing prevalence in the near future of Alzheimer's disease (AD) has been statistically predicted. As current pharmacological treatments turn out to be limited for the long-term clinical effects accompanying various side effects and complications, new schemes are in urgent need of a relatively safer and more effective treatment. In recent years, neuromodulation technologies such as optogenetics, transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), transcranial electrical stimulation (tES), deep brain stimulation (DBS), and focused ultrasound (FUS), which are proven with potential remedial effectiveness in several mental diseases, emerge to be a prospective therapeutic strategy for AD. By applying optical, magnetic, as well as electronic technology, modulations on specific brain regions can be achieved. And by applying ultrasonic technology, the process of medical molecules passing through the brain-blood barrier (BBB) can be facilitated. This article summarizes the current knowledge of some main neuromodulation technologies and provides insight into their possibilities for clinical application. By further illuminating the clinical effects, advantages, and limitations of these technologies, the article may help to guide clinical practice and enlighten new ideas for therapeutic strategy in AD.

Keywords: neuromodulation; Alzheimer's disease; technology; therapy.

1. Introduction

Alzheimer's disease is widely known as a neurodegenerative disease featured with characteristic clinical symptoms including progressive reduction of cognitive abilities, as well as abnormal mental and behavioral expression. Typically the pathology of AD is presented as cerebral atrophy along with accumulation of amyloid β and over-phosphorylation of tau protein, which is associated with the granulo-vacuolar degeneration in neurons [1]. There have been around fifty million people suffered from AD-caused dementia by 2018, and it is presumed that the prevalence is about to triple by 2050 [2], which indicates AD becoming one of the most intractable diseases in the 21st century. As AD is currently the main cause of dementia, seeking more effective treatments for AD has aroused great attention. Previously scientists have made efforts to find targets for pharmacological treatment, however, there is still no medicine available for fundamentally reversing or slowing down the pathological process of AD [3]. Besides, apart from the side effects of the drugs, most permitted medicines require lifelong medication which results in poor treatment compliance. Considering the limitations of pharmacological treatment, more attention is now drawn to finding more possible strategies by applying neuromodulation technologies.

Neuromodulation technology has achieved great progress during the past decades. It has not only provided new tools to study neural circuits and analyze functions of different brain areas but also given prospective strategies for the treatments of several mental diseases. Neuromodulation is a biochemical engineering technology that functions on alternations in the specific process of neural signal transmission mostly by means of optical, magnetic, electronic, or ultrasonic stimulation, and results in the regulation of activities of specific groups of neurons and changes of the specific cerebral functions [4]. In this way, neuromodulation can be possible to interfere with abnormal cerebral neural networks inside patients with AD and thus slow the progression of AD. Compared to traditional pharmacological treatments, neuromodulation has the advantages of fewer side effects and complications for long-term treatments. For patients with functional lesions of the liver or kidney, or with a gestational state, neuromodulation is a safer therapeutic strategy to attain better clinical

outcomes. The aim of this article is to summarize the functional mechanisms, clinical effects, advantages, and limitations of main neuromodulation technologies applied or prospectively to be applied clinically, and enlighten new ideas and strategies to be explored in clinical trials in the future.

2. Neuromodulation Technologies applied in Alzheimer's Disease

2.1. Optical Neuromodulation Technology

2.1.1 Optogenetics

Optogenetics is the combination of genetic techniques and optical tools, which can control neural activities in living tissues. It has high specificity in time, space, as well as cell types. In this technique, lenti- and adeno-associated viral vectors are the most commonly used carriers to transfer opsin genes into target neural cells. The target cells are then able to express photosensitive proteins, which can be activated by different wavelengths of optical stimulation to excite or inhibit the activities of these target cells. In this way, optogenetics can precisely modulate the activation of specific neurons and related neural circuits.

As a research tool, benefiting from its optical properties, optogenetics enables the understanding of connections between a specific series of memories with specific brain areas, which helps to illuminate memory circuits impaired in AD. As a potential strategy for clinical treatment, a previous study has manifested its effectiveness in the enhancement of spatial learning, memory restoration, and synaptic plasticity in experimental mice [5]. In another study, researchers demonstrated that activating glutamatergic neurons by optogenetic tools in the bilateral dentate gyrus in patients with AD can result in advancements in learning behavior and short-term memory restoration, which may be associated with increased glutamate receptors in the hippocampus [6]. The mammillary body (MB), the anterior thalamic nuclei (ATN), and the nucleus Re are currently the representative feasible brain sites for optogenetic-mediated therapy. Apart from regulating neural activities in the neural network of memory formation, optogenetics can also directly function on memory engram cells which are critical compositions of memory storage. As memory engram cells of specific series of memory are marked by optogenetic viruses, memory retrieval can be induced by optical stimulation on these marked engram cells [7].

To be mentioned, although optogenetics has the advantages of high specificity, better sensitivity, and precise functional target which seemed to be promising, it is still alongside concerns of clinical safety as it is an invasive technology carried with viruses. Non-viral vectors like plasmid and liposome are also available for gene transfer, but these vectors mostly lack delivery efficacy and expression rates [8]. Therefore, it is important to weigh the benefits of higher clinical effectiveness by applying viral vectors against the safety issues. Also, the development of wireless optogenetic technology and nano optogenetic technology provide a less invasive solution for neural circuit modulation.

2.1.2 Photobiomodulation (PBS)

PBS is potentially an advanced non-invasive neuromodulation technology for treating multiple central nervous system diseases by delivering invisible light or near-infrared light to the target brain regions to interfere with the neurodegeneration process. To implement this technology, the frontal cerebral regions or midbrain regions are exposed to electromagnetic radiation with a low power approximately between 1mW and 1W for stimulation. In this process, a photoreceptor or a molecular chromophore is applied to absorb photons. By creating a conformational change in the molecule, PBS can lead to multiple photo effects including stimulation of metabolic transmission in cerebral tissues, increase of intracellular adenosine triphosphate generation, synapse restoration, and so on which provide critical effects on improving AD pathological states and cognitive levels [9]. Also, it's been found that PBM can modulate gut microbiota flora and thus affect the brain-gut axis which is presumed important in neurodegeneration in AD [10].

The consensus on the clinical effect of PBS has been reached for the reduction in the accumulation of amyloid proteins, which indicates the potential application for AD is quite possible. However, by now PBS is not an approved therapeutic strategy for clinical use. In a study, a lack of post-clinical effectiveness was reported [11], which indicated that patients who receive PBM-based therapy may be acquired for persistent PBS to attain long-term beneficial effects. Therefore, further research on PBS is needed for a comprehensive understanding of the fundamental mechanisms of treating neurodegenerative diseases like AD.

2.2. Magnetic Neuromodulation Technology

2.2.1 Transcranial Magnetic Stimulation (TMS)

TMS is a non-invasive technology applied in the treatment of various neurodegenerative diseases. Based on Faraday's law of electromagnetic induction, the functional mechanism of TMS relies on electromagnetic pulses that can penetrate the skull to the target cerebral cortex by mainly applying electric pulse generators and magnetic coils. The effect of TMS varies according to the operation frequency, intensity, and patterns of electromagnetic impulse, among which the patterned repetitive TMS (rTMS) is the most commonly used technique, in which stimuli of equal-intensity electromagnetic pulses are given within deterministic time intervals for some time. rTMS can be classified into categories including high frequency (over approximately 5 Hz), low frequency (under approximately 1 Hz), and other types of stimulation bursts. By Meta-analysis, researchers found that generally higher frequency increases cortical excitability whereas lower frequency inhibits cortical excitability, but this is not a rule fitting in all situations [12]. Thus, it is deemed that higher frequency may result in better long-term therapeutic outcomes in the improvement of cognitive ability.

rTMS has been found effective for improving cognitive states in Alzheimer's disease [13]. Compared to optogenetics, rTMS is non-invasive and safer for clinical treatments, and rTMS-related effect-evaluation studies have stepped into clinical trials which crossed the limitation where experimental mice cannot fully represent neural modulation effect in humans. The most commonly used brain region for rTMS is the dorsolateral prefrontal cortex (DLPFC), which has a close bio-connection with the hippocampal region in the neural network related to memory storage. Other target regions such as the left parietal cortex and Broca region are also available to improve cognitive ability in AD [14]. The long-term clinical outcomes of rTMS rely on the combination of different parameters including inter-stimulus interval, number and intensity of stimuli, stimulus duration, delivery mode, and so on. Yet there is no coincidence in certain parameters for therapeutic schemes, thus clinical trials with larger samples are acquired to guide its practical use.

According to current knowledge, rTMS with higher frequency, multi-target, as well as a combination with cognitive training has a more promising therapeutic effect, but the results need further verification due to statistical instability from small samples of clinical trials and the influence of individual variations.

2.2.2 Magnetic Transformation Nanoparticle Mediated Magnetic Neuromodulation

The most concerning problem of TMS is its limitation for precise spatial localization for electromagnetic stimulation. Previously magnetic nanoparticles were developed to provide a solution, which is by the utility of the mechanical force converted from energy of the magnetic field, the magnetic nanoparticles are able to attach to target biomolecules and organelle, and by activating mechanical-force-sensitive ion channels of transient receptor potential vanilloid (TRPV), these nanoparticles can increase neural activities in the specific brain region. Researchers further package magnetothermal conversion nanoparticles into thermosensitive liposomes. Under thermal energy generated in the magnetic field, the nanoparticles release N-clozapine oxide (CNO) which is combined with certain kinds of receptors and finally activates specific neurons [15].

This magnetic neuromodulation technology optimizes the traditional magnetic neuromodulation technology in its positioning accuracy, and it provides functional modulation in deep brain regions. But it also has common safety drawbacks of invasive penetration.

2.3. Electrical Neuromodulation Technology

2.3.1 Deep Brain Stimulation (DBS)

DBS is an invasive neurosurgical technique that modulates neural activities by applying stimulating electrodes, subcutaneous leads, and pulse generators implanted in specific target brain regions. Usually, the bio-compatible stimulation electrodes are placed in multiple angles and positions in the brain [16]. Compared to conventional stimulation electrodes, directional electrodes allow more various shapes of the electric field. Also, the development of the film printing technique enables flexibility in designing more possible electrodes. Some hypotheses propose potential mechanisms of DBS functional mechanism in AD, including modulation in neural electrical activities, neurogenesis promotion, as well as release of certain neurotransmitters, but the exact mechanism remains unknown.

With the development of the stereotaxic technique and the imaging technique, DBS has become a prospective strategy applied in the treatments of dementia, chronic pain, major depression, and memory disorders in AD. Different target cerebral regions in human clinical trials have been explored based on various neural circuits related to AD. To be specific, the ventral capsule/ ventral striatum participates in the frontal lobe neural network, intralaminar thalamic nucleus and midline thalamic nuclei are crucial compositions forming neural pathways between the cortex and the thalamus, nucleus basalis of Meynert play an important role in cholinergic circuit locating in the base forebrain, and in the critical Papez circuit includes target regions such as the fornix, anterior nucleus of thalamus, and mammillothalamic tract [17]. Based on results from clinical trials, DBS has shown promising intervention neurodegeneration, and clinical results are observed positive in early-stage AD as well as patients at a young age [18].

Generally speaking, DBS is a safe and effective technology that has a promising future for therapeutic strategy in AD. Though there are commonly used parameters including stimulation frequency in 130/20 Hz, long-term duration, voltage of 3.0-3.5 V, patterns of bilateral stimulation, and pulse width in 90-150 μ s [18], further verification based on larger samples is acquired to evaluate an optimal choice for clinical applications.

2.3.2 Vagus Nerve Stimulation (VNS)

VNS is another electrical neuromodulation technology that can be implemented either invasively or non-invasively. The most important target region for VNS is the locus coeruleus, a critical original region constantly providing norepinephrine within the central nervous system. The progressive neurodegeneration process in the locus coeruleus can result in the reduction of norepinephrine and lead to inflammatory pathological changes in cerebral areas, which is supposed to be a major factor contributing to pathological progress in AD. By activating neural activities in the locus coeruleus and promoting the release of norepinephrine, VNS can reduce inflammatory signaling in the cortex and the hippocampus, thus slowing pathological progression. The implanted vagus nerve stimulation (iVNS) is an invasive surgical technique that has been approved for clinical use. Usually, apparatuses of iVNS are surgically implemented in the thorax beneath the clavicle to directly stimulate the cervical vagus nerves [19], which possess the technology with high spatial specificity and accuracy. However, it is inevitable for invasive technology to face problems of various complications and side effects including hematoma, headache, and infection. On the contrary, transcutaneous vagus nerve stimulation (tVNS), a non-invasive technique, has the advantage of avoiding such issues. tVNS can usually be implemented superficially on the ear or in the neck. Both iVNS and tVNS can modulate LC by activating either afferent or efferent vagus nerve fibers to provide neural protection and are demonstrated to induce a promotion in salivary α amylase concentrations [20].

By now, VNS is clinically applied in treating refractory epilepsy which has confirmed no responses to drug therapy and with no indication for traditional surgical treatments [19]. iVNS has shown satisfactory clinical effects by improving cognitive levels, enhancing visual attention, and bettering memory performance. Especially for those who are still in the early stage of AD, VNS may provide a pathway to restore phasic LC firing [21]. According to clinical feedback, although the non-invasive

tVNS technology has fewer side effects compared to iVNS, iVNS is still deemed to lead a more obvious clinical outcomes where the vagus nerves are stimulated directly by electrodes and have a more prospective potential for closed-loop modulation. Therefore, reassessments for the leverage of iVNS and tVNS are needed for clinical decisions.

Based on present clinical results, VNS can provide a remarkable enhancement in memory behavior and cognitive level. However, the balance between better clinical outcomes and less invasive harm requires a rethought. Also, relative parameters such as duration, intensity, and time interval of stimulation are acquired optimization for further individualized therapeutic strategy.

2.3.3 Transcranial Electrical Stimulation (tES)

tES is a non-invasive technology for neural activity regulation. By setting electrodes on the head, weak electrical current can be passed into specific brain regions thus modulating its neuronal activities. Transcranial direct current stimulation (tDCS) is a typical pattern of tES, which is applied by delivering a constant, low-intensity current to the brain surface. In this way, tDCS can up- or down-regulate trans-membrane potential thus modulating cortical excitability. According to different forms delivering the current, tDCS is classified into two types, including positive anodal transcranial direct current stimulation and negative cathodal transcranial direct current stimulation [22]. The anodal tDCS can up-regulate cortical excitability by improving depolarization of neural membrane potential whereas the cathodal tDCS can down-regulate cortical excitability by raising the threshold of neuronal excitation.

Based on a Meta-analysis of clinical trials, monolingual treatment of tDCS has a better improvement in cognitive function in AD [23]. Also, upon various target regions for tDCS, stimulation on the temporal cortex can remarkably improve cognitive levels compared to left DLPFC. Besides, stimulation on the bilateral temporal cortex observably improves accuracy in memory tasks compared to the bilateral frontal lobe [24]. It's been demonstrated in both short-term and long-term clinical trials that anodal tDCS is effective in enhancing cognitive levels and slowing down the neurodegeneration progression in AD [25]. Pathologically tDCS can benefit the reduction of amyloid accumulation, which indicates the possibility for tDCS to be applied in the early-stage AD. In another study, the experimental mice significantly improved abilities of spatial learning and memory restoration, although no recovery in recognition abilities has been shown [26].

Although by now tDCS is not approved for clinical treatments in AD, current experiments and trials have given promising potential in treating AD, especially in the early stage of its pathological progression. To certify this possibility, more clinical trials are needed and operators should always be aware of possible complications in the meantime.

2.4. Ultrasonic Neuromodulation Technology

2.4.1 Focused Ultrasound (FUS)

FUS is another non-invasive technology that modulates brain function by accurate thermal-reliable or non-thermal-reliable stimulation. According to intensity, there are generally two forms of FUS, which are high-intensity focused ultrasound (HIFU) and low-intensity focused ultrasound (LIFU) [4]. By generating strong heat in specific brain regions, HIFU can cause ablation to the local tissues, which is currently approved for clinical use in improving refractory essential tremor but is accompanied by a series of complications such as headache, paresthesia, and gait disturbances. In contrast, LIFU regulates neuronal function and activation of neural circuits with no damage to neurons.

Apart from modulating neuronal activities, neuromodulation technology may work in another way for the treatment of mental disorders, which is facilitating therapeutic intracranial drug delivery by opening the blood-brain barrier (BBB). The BBB is a highly selective filter membrane that can restrict plenty of therapeutic medical molecules from circulating extracellular cavity and passing into the brain physiologically. To solve this problem, magnetic resonance-guided focused ultrasound (MRgFUS) applied by using a combination of LIFU and micro-bubbles, is emerging to be an effective

tool aiding in pharmacological treatments within the brain. Basically by giving an ultrasound wave, the micro-bubbles injected intravenously are able to expand. As the micro-bubbles meet the BBB, they can lead to allosteric changes which results in stretching out of the structures and the opening of this barrier for a temporary moment[27]. So far, many therapeutic agents such as antibiotics have taken advantage of this technology and are investigated across the BBB into specific target brain regions to treat multiple mental diseases including AD. Also, in most of the current preliminary clinical trials, this technology is reported with only mild side effects which manifests its safety for practical use [28].

Currently, FUS is approved for clinical use in several mental diseases. However, the underlying mechanism in the function of ultrasonic stimulation modulating brain activity is still unclear, which limits its further clinical application in AD to some extent. Also, larger samples of clinical trials may be needed for evaluating clinical effects in AD and exploring a higher spatial specificity mode of FUS.

3. Discussion

Progressive memory loss and reduction in cognitive level resulting from AD not only have the patients living with difficulties adapting to normal life but also bring quite much sorrow to their families. By applying neuromodulation technologies to experimental or clinical trials, great potential in AD treatments of these technologies has been found. However, therapy based on neuromodulation technology is yet immature. For further study, a deeper understanding of the underlying mechanism in the process where these technologies function in improving pathological disorders in AD is needed for the purpose of confirming a relatively more effective target brain region for stimulation. Also as many of the neuromodulation technologies are currently not officially approved for clinical use, evaluation and optimization are still needed by considering the safety issues, long-term effectiveness, as well as cost for practical application.

In addition, larger-sampled studies and statistical analyses are needed for comparisons between invasive and non-invasive technologies as well as optimization of operation parameters. Normally invasive technologies are accompanied by various side effects and complications due to surgical implementations, but they are also assessed with high spatial specificity and sensitivity. Whereas non-invasive technologies are comparably safer in avoiding those surgical-related side effects but are weaker in specificity and sensitivity to target cerebral regions which leads to less ideal clinical outcomes. Therefore, a more comprehensive evaluation is needed to leverage the advantages and limitations of invasive and non-invasive neuromodulation technologies. Furthermore, although there is a consensus on the approach to operating these technologies, current statistics of the operation parameters and clinical results are quite unstable because of all kinds of variations in the small-sampled experiments and trials. In this case, reassessments of the clinical effect and optimization of operation parameters are needed on the basis of large-sampled, multi-center, double-blind, and randomized controlled studies.

To be mentioned, it is exciting that with the development of some burgeoning technologies especially like stereotaxic technique, neuroimaging, and artificial intelligence, increased efficacy and efficiency of neuromodulation technology can be achieved by the application of multi-technology intersection. The combination of these new technologies along with biomarkers may also help diagnosis of early-stage AD, which will provide an earlier time-point for treatment and thus probably lead to a more ideal clinical outcome. Besides, based on current knowledge of these technologies, it is hopeful to explore a low-risk multi-model therapeutic strategy for AD treatment.

4. Conclusion

AD is a neurodegenerative disease gaining a worldwide increasing prevalence rate. As pharmacological treatment has limitations on long-term clinical effects and is observed with poor

treatment compliance on lifelong medication, neuromodulation technology is gradually becoming more hopeful for therapeutic strategy.

According to multiple clinical trials and experimental research, improvements in memory behavior and cognitive level can be induced by implementing technologies such as optogenetics, VNS, DBS, tDCS, and rTMS. There are also several technologies providing potential mechanism-based possibilities to modulate neuronal activities and slow the pathological progression such as PBS and nanoparticle-mediated magnetic neuromodulation technology. Also, MRgFUS is mentioned to be a promising auxiliary technology for AD treatment by aiding medical molecules through the BBB, though currently the technology is still limited due to a lack of effective long-term medicine for AD.

As research on neuromodulation technologies is mostly small-sampled, the clinical effects and operation parameters need further statistical reassessment on larger-sampled, multi-center, double-blind, and randomized controlled studies to optimize the specificity and sensitivity of the therapy. Moreover, a deeper understanding of modulation mechanisms, comparisons of different technologies, re-evaluations on safety issues, as well as explorations of multi-technology intersections are needed for the optimization of therapeutic strategy. By exploring specific target regions, effective operation parameters, multi-model therapy, as well as low-risk strategies, neuromodulation technology is prospective to play a critical role in AD treatment in the near future.

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