Status of Noninvasive Brain Stimulation in the Therapy of Alzheimer's Disease

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Alzheimer's disease (AD), characterized by progressive memory impairment and dementia leading to severe deterioration of daily living, has been a public health crisis that currently lacks effective treatments. The reported prevalence of AD was 3.21% in people aged ≥65 years.[1] More than 7 million people live with AD in China today and the number continues to increase. AD imposes a heavy financial burden on the society and it is becoming worse. The total socioeconomic costs of Chinese patients with AD was estimated to be US $167.74 billion in 2015 and is predicted to reach US $1.89 trillion by 2050.[2] There are currently five drugs approved by the U.S. Food and Drug Administration for the treatment of AD. However, the pharmacological treatments have limited efficacy, even if applied during the early stages, and none of the available treatments can alter the underlying course of the disease.[3] Given the failure of numerous clinical drug trials, alternative therapeutic approaches have been investigated to slow down the disease; one such alternative therapeutic approach is noninvasive brain stimulation (NIBS).

New Concept for Alzheimer's Disease: A Dysfunctional Brain Network

In many studies, impaired synaptic function in the hippocampus was found to appear before amyloid plaque burden and neuronal cell death.[4-6] The extent of cognitive impairment correlated better with synaptic loss than with Aβ plaques or neurofibrillary tangles.[4] Memory processing has been found to be triggered in alignment with the theta oscillations in the hippocampus.[7] In summary, an increasing number of findings support the notion that AD is more than a disease about Aβ plaques.

With the continued advancement of neuroimaging and brain network analyses, it is possible to consider the development of AD from a new perspective. AD is characterized by extensive changes in the brain with a tendency to interfere with memory-related networks. An increasing number of studies have demonstrated that the topological properties of global networks and core neural circuits in AD are dysfunctional and lead to a loss of information transfer efficiency and a decline in processing speed.[8-12] The most notably involved networks are the default-mode network and the frontoparietal network. They are critical for memory and executive functioning, respectively.[13,14] Therefore, disruption and disconnection in these networks may be responsible for cognitive and behavioral impairments in AD. Given the potential of NIBS to modulate and improve information transfer efficiency and integration, it would be reasonable and promising to explore NIBS treatment in AD to minimize cognitive problems and ultimately to slow down the progression of the disease. In fact, brain network-based neuromodulation provides a new treatment not only for AD but also for other functional brain disorders, such as depression and epilepsy. In these diseases, the targets could

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be located based on pathophysiological changes in involved networks, such as left dorsolateral prefrontal cortex (DLPFC) which is synaptically connected to the limbic system involved in mood regulation and epileptogenic foci which is hyperactivated in epileptic network.

Advent of an "Era of Noninvasive Neurostimulation"

The NIBS provides a promising tool to noninvasively modulate dysfunctional brain circuits. Repetitive transcranial magnetic stimulation (rTMS) changes cortical excitability and modulates brain activity across distributed neural networks beyond the duration of stimulation itself.[15] More recently, a new pattern of rTMS, called theta burst stimulation (3 pulses at 50 Hz repeated at 200 ms intervals), has been developed as a method to induce long-lasting changes in cortical excitability with less stimulation. Transcranial direct current stimulation (tDCS) changes the resting membrane potential of neuronal populations around the electrodes and has been shown to have a long-lasting effect.[16] In the last century, these young NIBS techniques developed and were gradually maturing. The preliminary exploration of their mechanisms and applications in clinical practices showed promising results at this stage. There is growing interest in NIBS as a means to ameliorate symptoms and the course of neurological diseases. In the last decade, a great number of clinical trials have been performed, and clinical guidelines have been published over the past 4 years.

In the treatment of AD, several trials and reviews have suggested that rTMS and tDCS may be beneficial for various cognitive functions in patients with AD, although no recommendation can currently be made.[17] It should be emphasized that the reported studies used different protocols of stimulation, which may result in different outcomes across studies. In the reported studies, the main target explored was the DLPFC, which was shown to be involved in the decline of cognitive functions such as working memory and executive function in AD patients.[18,19] In the largest controlled clinical trial that enrolled 45 patients, high-frequency rTMS over the DLPFC significantly improved the Mini–Mental State Examination (MMSE), the Instrumental Activities of Daily Living Scale, and the Geriatric Depression Scale.[20] Comparatively, the studies with tDCS were limited and had small sample sizes. In a crossover controlled trial on ten AD patients, a single session of anodal tDCS was applied over the left DLPFC and left temporal cortex and showed an enhancement on the visual recognition memory (VRM) task. In most rTMS studies, the frequency was generally set at 20 Hz or 10 Hz, and the intensity was 90% resting motor threshold (rMT) or 100% rMT. In tDCS studies, the intensity was generally 1.5 or 2 mA lasting 15 or 30 min. Repeated stimulation sessions are advised for a sustained effect,[20,21] although an immediate effect has been found in a single-session treatment.[22-25] Moreover, as AD is characterized by the deterioration of multiple cognitive functions involving a variety of different neural networks, delivering stimulation to modulate specific brain networks has been explored and has shown enhancement of cognitive abilities related to specific brain functions. For example, Boggio *et al*. applied anodal tDCS over the bilateral temporal cortex for 5 days and found that AD patients improved their performance at the VRM task but not at the visual attention task (VAT) or MMSE.[21] Cotelli *et al*.[26] found an improvement in auditory sentence comprehension in healthy older adults when high-frequency rTMS was applied over the left DLPFC and an improvement in action-naming task when rTMS was applied over the bilateral DLPFC. Notably, in a study by Ahmed *et al*., a clinical benefit was present only in mild and moderate AD patients and not in severe AD patients. These findings indicated that the efficacy also depends on disease severity.[20]

All the attempts succeed in pointing out the possibility of using NIBS treatment in AD, although there is still a long way to go. In the near future, progressive improvements and innovations in technology, methodology, and conceptual understanding will lead to breakthroughs in therapeutic performance for AD.

Potential Pathophysiological Mechanism of Noninvasive Brain Stimulation in Alzheimer's Disease

Despite the promising therapeutic effect of NIBS in AD, the exact mechanism is still not completely understood. The assumption in AD that cognitive and behavioral impairments are related to disruption and disconnection in the brain network makes neurostimulation a potential therapeutic intervention. However, it is unclear how neurostimulation modulates the disrupted and disconnected network at the neurophysiological level. Some neurophysiological studies in AD patients, such as short-latency afferent inhibition (SAI) and paired-pulse TMS, showed abnormalities of cortical excitability. A significant reduction in SAI was found in AD and is correlated with the degree of memory impairments, which could be probably explained by the cholinergic dysfunction in temporo-limbic areas. The rMT, cortical silent period and short-interval intracortical inhibition are generally reduced in AD, and they could be interpreted as increased motor cortex excitability.[27,28] Taken together, the neurophysiological studies have demonstrated that motor cortex excitability is enhanced in AD. It is speculated that glutamatergic transmission dysfunction is involved in the pathogenesis of cortex excitability. However, the question is why neurostimulation treatment is aimed at increasing cortical excitability (high-frequency rTMS and anodal tDCS) in AD patients who show cortex hyperexcitability. It is hypothesized that hyperexcitability may result from other pathophysiological mechanisms, such as reduced synaptic efficiency or hypoplasticity.[29] Additionally, the overall effect of neuromodulation depends on the state of the brain; therefore, the exact effect of high-frequency rTMS and anodal tDCS in AD patients remains debatable.

Safety

In 2014 and 2017, the International Federation for Clinical Neurophysiology published the guidelines on the therapeutic use of rTMS and tDCS, respectively. The side effects of NIBS are rare. The precise risk ratio of TMS-associated seizures is unclear but is thought to be <1/1000 studies.[17] Other side effects of TMS include mild headache or neck pain, tinnitus, and acute psychiatric effects. tDCS is also associated with minor side effects. Itching and burning sensations, mild headache, appearance of flashes of light at the start/end of the stimulation have been reported. In short, the safety profile of NIBS is quite favorable as long as it is utilized within the parameters based on the current recommendations.

The Way Forward

Closed-loop patterns

To date, NIBS has been performed in an open-loop manner in which stimulation is delivered continuously regardless of the performance by the patient. However, the rhythmicity and timing of stimulation may be crucial for more physiologically relevant functional activation of memory-related networks. For example, memory acquisition, encoding and retrieving phases encompass different neurophysiological phenomena,[7] and neuromodulation should be appropriately timed relative to different phases. Additionally, in behaving animals, long-term potentiation is preferentially induced at the peak of local theta rhythm in hippocampi, and long-term depression is induced in response to stimulation at the trough.[30] Therefore, novel devices need to be developed to stimulate in a closed-loop pattern and controlled by behavioral feedback and brain signals.

New stimulation techniques

In addition to tDCS and rTMS, there are some other novel promising stimulation techniques that have been developed recently. Transcranial ultrasound stimulation (TUS) has a spatial resolution of approximately 2 mm and does not require exogenous factors or surgical invasion.[31] As a form of genetic therapy, optogenetics has unrivaled spatial and temporal precision of controlling specific neuronal populations and thereby allows for the direct control of cerebral activity.[32] New stimulation devices based on TUS and optogenetics might be invented to treat neurological diseases with better efficacy and safety, although this area still faces many obstacles. Transcranial alternating current stimulation (tACS) is another NIBS technique that influences endogenous brain oscillations. In healthy subjects, tACS in the theta frequency range improved reversal learning when applied over the frontal cortex[33] and multitasking performance when applied over the prefrontal cortex.[34] Electroconvulsive treatment (ECT) is an effective treatment for major depression, mania, schizophrenia, and catatonia. In studies of ECT for elderly depression, an improvement on the MMSE was found,[35] although additional ECT data with AD patients are still needed. Magnetic seizure therapy (MST) is a new treatment for neuropsychiatric diseases. The limited available studies have shown that MST might improve cognitive function (e.g., verbal learning) in patients with depression.[36,37] However, it cannot be excluded that the improvement in cognition may result from the improvement in depressive symptoms. Noninvasive VNS can stimulate the vagus nerve indirectly through the skin of the neck or ear. It enhanced cognitive functions assessed by the MMSE and Alzheimer's Disease Assessment Scale-Cognitive subscale in a long-lasting manner.[38,39] However, there are a very limited number of studies.

Large randomized controlled trials

The results of NIBS in AD have varied across studies, mainly due to the various stimulation protocols. With the increasing number of randomized controlled trials, senior NIBS centers are needed to lead larger, multisite proof-of-principle studies with proper sham-stimulation controls. In the future, clinical trials with large sample sizes with similar stimulation protocols and standardized memory assessment are required to ascertain the true efficacy and safety. Based on these randomized controlled trials, the guidelines for NIBS in AD also need to be published.

Stimulation technological improvements

Novel stimulation strategies and techniques are warranted to enhance the efficacy of treatment. First, the neurostimulation that targets multiple brain regions engaging in cognitive training of their various supported cognitive functions would be most promising.[40,41] A combination of multiregional neurostimulation and cognitive training therapy may produce beneficial synergistic effects beyond each therapy alone. Second, the development of rTMS neuronavigation techniques[42] allows the use of subject-specific functional neuroimaging data to accurately guide the placement of transcranial magnetic stimulation coils and therefore selects targets based on their relationship with specific cognitive function or its connectivity with other regions. Third, a combination of tDCS and rTMS could be explored to achieve maximum benefit. For the sake of different mechanisms of electrical and magnetic stimulation, sequential time patterns or even simultaneous stimulation may produce a synergistic effect. Fourth, a multichannel stimulator might be developed, which may help to modulate multiple brain regions in a specific pattern, such as in a fixed time sequence. Fifth, deep NIBS via temporally interfering electric fields in animals was recently reported. Hopefully, the deep NIBS in humans may be realized in the near future. Last, miniaturization of the stimulation systems is also needed. Home-based devices that can be used adequately outside a medical facility or hospital by patients' caregivers may be developed, such as home-based tDCS.[43]

Standardized noninvasive brain stimulation system

Last but not the least, it is warranted to establish a standardized NIBS system, which should include senior NIBS centers, primary NIBS centers, and family medicine

as well. This NIBS system could provide comprehensive and long-term NIBS treatment for AD patients. The senior NIBS centers guide intervention on the basis of individual cognitive domains and establish stimulation settings for patients. The primary centers or even patients' caregivers provide long-term NIBS treatment.

In conclusion, AD poses one of the most medical challenges of this century, with an increasing number of afflicted individuals worldwide. Fortunately, a bridge between the basic scientific knowledge of the brain networks associated with AD and network-based NIBS has been built up in the past decades. The distance between clinical trials and technical improvements to clinically applicable devices that could treat the cognitive impairment and ameliorate the disease course is still long. Over the next decade, efforts should continue to characterize the innate characteristics of the networks involved in AD, both the individual parts of the network and larger levels of dynamic changes across the network, and to invent noninvasive, highly efficient, miniaturized, and standardized brain stimulation devices. Over time, reliable results from ongoing clinical trials will be reported, and the ideal stimulation targets and paradigms for the treatment of AD will be further elucidated. The standardized NIBS system needs to be established to provide comprehensive treatment services for AD patients. Furthermore, the concept of guiding NIBS based on brain networks might not only lead to the treatment of AD, but also many other neurological diseases that could be considered diseases with "disturbed function of brain networks."

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