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Research Article

Progress in Facilitating Therapy for Alzheimer's Disease: Non-Invasive Treatment

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Abstract

With the aging of the global population, the number of Alzheimer's disease has increased rapidly. Alzheimer's disease has become one of the major diseases affecting human health, and no drugs can reverse its progression. Because of its unclear etiology and complex pathological mechanism, the newly developed single target drugs do not work well in clinical trials. Recently, more and more studies have shown that some non-invasive stimuli, such as light therapy, transcranial direct current stimulation, repetitive transcranial magnetic stimulation, physical activity, intermittent hypoxic training and others can improve the cognitive behaviour and pathological changes of Alzheimer's disease. Here, we review the research progress of these non-invasive therapies in the treatment of Alzheimer's disease and discusses their potential application.

Keywords: Alzheimer's disease; Light therapy; Repetitive transcranial magnetic stimulation; Transcranial direct current stimulation; Physical activity; Intermittent hypoxic training

Introduction

Dementia and severe cognitive impairment are very closely linked to ageing [1,2]. With the aging of the global population, the population of Alzheimer's disease (AD) is expected to fourfold by 2050 [3]. The main neuropathological characteristics of the AD brain are extracellular neurotic plaques which is Aβ deposition and intracellular neurofibrillary tangles which is the hyper phosphorylated accumulation [4]. These pathological changes are often accompanied by reactive microglial proliferation and loss of neurons and synapses [3]. Cognitive decline, emotional, behavioural and sleep disorders, as well as restrictions on activities of daily living, often increase the burden on AD patients and their caregivers [5]. Efforts need to be made to improve the national dementia care system, strengthen the skills and knowledge training of medical personnel, and actively carry out global cooperation to prevent and treat the disease [6-9]. Existing medical treatment for AD have limited effectiveness, expensive, and sometimes causing serious side effects. Therefore, alternative or complementary adjuvant treatment strategies, such as light therapy, transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), physical activity and intermittent hypoxic training (IHT) etc, have gained more and more attention. As a new noninvasive brain stimulation method, neuromodulation technology has attracted more and more attention in the treatment of AD cognitive impairment [10].

Light therapy

Light therapy is a kind of non-invasive non pharmacological treatment method, with different wavelengths, intensities, durations and different region in application. Many researchers find that low-power laser photo biological could attenuate Aβ-induced cell apoptosis [11,12]. It is found that light therapy can increase ATP and mitochondrial membrane potential, reduce intracellular calcium concentration and lighten oxidative stress. This may be the reason why phototherapy plays a beneficial role in central nervous system diseases [13]. Let's take a look at its application in AD at (Table1).

Bright light therapy

Bright light therapy has a certain effect in improving cognitive and noncognitive symptoms of dementia [14]. Specifically, firstly, there is a statistically significant increase in MMSE total scores after bright light therapy [15]; Secondly, it causes an effective intervention for depression in both mild/moderate and severe dementia [16]. Depression is widespread in the elderly and may be an early manifestation of AD [17]; thirdly, the application of bright light therapy consolidates sleep and strengthens diurnal rhythms in dementia [18-20]. It is worth mentioned that, the latest research shows that sleep maybe a biomarker of tau and Aβ burden in human brain [21]. Last but not least, even in severe dementia, bright light can improve behavioural symptoms and activity rhythm disturbances [22,23]. However, the biological mechanism by bright light therapy remains to be elucidated.

Different wavelengths

According to the reports, red to infrared light therapy (λ=600-1070 nm), and particularly light in the near infrared wavelength range, is becoming a relative safe and effective treatment therapy, which is capable of preventing neuronal death [24]. Also, low-power laser irradiation (λ=632 nm) has been applied to the spinal cord, which helps recover the relevant insured peripheral nerve [25].

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These suggests that light with different wavelengths may play a useful role in AD. Light-emitting diode (λ=630nm) reduces brain H2O2 levels and reverses age-related memory disorders in SAMP8 (senescence-accelerated prone 8 mouse, a model of age-related dementia) [26]. There are many statements mean that non-invasive light therapy (λ=670 nm, 808 nm, 1072 nm) reduces AD-related pathologies in the brain of animal model, near infrared light treatment is related to the reduction of hyper phosphorylated tau, neurofibrillary tangles, the size and number of amyloid-β plaques and the expression of inflammatory markers [27-30]. In mild to moderately severe dementia, research workers apply light-emitting diode devices combining transcranial plus intranasal photo biological regulation (810 nm) to treat the cortical nodes of the DMN (bilateral mesial prefrontal cortex, precuneus/posterior cingulate cortex, angular gyrus, and hippocampus), find that it improves cognitive ability significantly [31].

Specific frequency

The Tsai team recently reported that non-invasive scintillation light (gamma entrainment using sensory stimulus or GENUS) in AD model mice can induce gamma oscillations, thus causing pathological changes in the visual cortex of mice [32] namely, non-invasive 40 Hz light-flicker treatment could reduce the levels of Aβ1-40 and Aβ1-42 in the visual cortex and reduced the plaque load in aged, depositing mice [33]. Not long ago, they designed auditory tone stimulation to induce gamma frequency in the brain, thus regulating nerve activity, the results shows that 7 days auditory stimulation improved the memory ability and reduced amyloid plaque in AC and hippocampus of 5XFAD mice [34].

Neurophysiological Techniques: Transcranial Direct Current Stimulation (tDCS) and Repetitive Transcranial Magnetic Stimulation (rTMS)

Not only light therapy, recently new neurophysiological tools, such as rTMS and tDCS, which apply noninvasive transcranial electrical or magnetic stimulation to regulate neuronal activity, has been introduced into basic and clinical research of brain science [35]. Let's take a look at their application in AD at (Table 2).

tDCS

Transcranial electrical stimulation with weak electric current may be a promising approach to modulate brain excitability with non-invasive, painless, reversible and regional advantage [36-38]. Its function can be realized by changing the current intensity and duration, tDCS is widely used in human neuro scientific and clinical research at present [39]. In the humans, tDCS is able to lead sustained cortical excitability [40] cognitive improvements after 10 sessions of anodal tDCS in patients with AD patients [41]. Daily tDCS over the dorsolateral prefrontal cortex for 6 months may improve or stable cognition and regional cerebral metabolic rate for glucose in AD patients [42]. After AD patients received tDCS treatment, they perform better on visual recognition memory tests [43,44] and word recognition memory [45] significantly improved.

rTMS

TMS is a non-invasive technique that can produce current induced cortical excitability. It is considered that the application of 10, 15 or 20 Hz rTMS over the left dorsolateral prefrontal cortex, in the range of 10-15 successive sessions and 80-110% of individual motor threshold, is most probably to get rise to significant cognitive amelioration [46,47] and beneficial effects sentence comprehension [48]. There is a good deal of evidence that TMS has been considered as a possible treatment method for the cognitive impairment in AD patients [49-52]. Not only that, After 3 weeks of treatment, the cognitive function, behaviour and function of AD patients can be improved, and the effect can be maintained for more than 4 weeks [53].

Research subject/Author/year	Method	Human subject research	Nonhuman subject research
PC12, SH-SY5Y, HEK 293T cell [11]	Low-power laser irradiation	/	Aβ (25-35)-induced apoptosis (-)
PC12, HEK 293 T cell [12]	Low-power laser irradiation	/	Aβ (25-35)-induced apoptosis (-)
Dementia patients [14]	bright light, 1000lux	MMSE (+), CSDD (+)	/
Demented patients [15]	bright light, 3000 lux	MMSE (+)	/
Demented patients [16]	bright light	DSAOA (+), CSDD (+)	/
AD patients [18]	bright light, 2500 lux	Sleep (+), Circadian rhythms (+)	/
AD patients [20]	bright light, 5000/2500 lux	NPI-NH (+)	/
Dementia patients [22]	bright light, 10000 lux	CGIC (+)	/
AD patients [23]	bright light, 5000-8000 lux	CMAI (+), BEHAVE-AD (+)	/
Dementia mouse model [26]	λ=630 nm	/	Cognitive (+)
AD mouse model [27]	λ=808 ± 10 nm	/	Aβ levels (-)
AD mouse model [28]	λ=1072 nm	/	Aβ levels (-)
AD mouse model [29]	λ=670 nm	/	Aβ levels (-)
AD mouse model [30]	Low-power laser irradiation	/	Aβ levels (-), Cognitive (+)
AD patients [31]	λ=810 nm	ADAS-cog (+), MMSE (+)	/
AD mouse model [32]	40 Hz light flicker	/	Aβ levels (-)
AD mouse model [32]	40 Hz light flicker	/	Aβ levels (-)
AD mouse model [34]	40 Hz auditory and visual GENUS	/	Aβ levels (-), Cognitive (+)

Table 1: Research summery of light therapy for AD.

Research subject/Author/Year	Method	Human subject research	Nonhuman subject research
AD patients [41]	tDCS, 2 mA	MMMSE (+), MoCA (+)	/
AD patients [42]	tDCS, 2 mA	MMSE (+), Boston Naming Test (+)	/
AD patients [43]	tDCS, 2 mA	visual recognition memory (+)	/
AD patients [44]	tDCS, 2 mA	visual recognition memory (+),	/
persists for at least 4 weeks	/	DSAOA (+), CSDD (+)	/
AD patients [45]	tDCS, 1.5 mA	word recognition memory task (+)	/
AD patients [47]	rTMS, 20 Hz	MMSE (+), IADL (+), GDS (+)	/
AD patients [48]	rTMS, 20 Hz	sentence comprehension (+)	/
AD patients [49]	rTMS, 20 Hz	naming performance (+)	/
AD patients [50]	rTMS, 10 Hz	MMSE (+)	/
MCI+AD patients [51]	rTMS, 10 Hz	TMT (+)	/
AD patients [52]	rTMS, 20 Hz	episodic memory (+)	/
AD patients [53]	rTMS, 5 Hz	MMSE (+), ADAS-cog (+), NPI (+)	/
AD rat model [54]	rTMS, 1 Hz	/	rescued deficits in LTP and spatial memory
AD mouse model [55]	rTMS, 1 Hz	/	reversed the impairment of spatial learning and memory
AD rat model [56]	rTMS, 5 Hz	/	Enhance BDNF-TrkB signaling in both brain and lymphocyte
AD patients [59]	rTMS-COG, 10 Hz	ADAS-cog (+), CGIC (+)	/
AD mouse model [34]	40 Hz auditory and visual GENUS	/	Aβ levels (-), Cognitive (+)

Table 2: Research summery of neurophysiological techniques for AD.

MMSE- Mini Mental State Examination; **CGIC**- Clinical Global Impression of Change; **CMAI**- Cohen-Mansfield Agitation Inventory; **BEHAVE-AD**- Behavior Pathology In Alzheimer's Disease Rating Scale; **CSDD**- Cornell Scale for Depression in Dementia; **ADAS-Cog**- Alzheimer's Disease Assessment Scale-Cognitive; **NPI-NH**- Neuropsychiatric Inventory, Nursing Home version; **DSAOA**- Depressive Symptom Assessment for Older Adults; **GENUS**- Gamma Entrainment Using Sensory Stimulus; **IADL**- Instrumental Daily Living Activity; **GDS**- Geriatric Depression Scale; **MCI**- Mild Cognitive Impairment; **TMT**- Trail Making Test; **NPI**-Neuropsychiatric Inventory; **MMMSE**- Modified Mini Mental State Examination (MMMSE); **MoCA**- Montreal Cognitive Scale.

Studies have shown that noninvasive rTMS treatment may effectively ameliorates cognitive and synaptic functions in AD mice model by reducing the Aβ neuropathology [54,55]. It has been reported that rTMS to cortex promotes BDNF-TrkB-NMDAR functioning in both cortex and lymphocytes in rats [56] and it also regulates the glutamate and gamma-aminobutyric acid systems [57].

Research shows that cognitive training (COG) may effectively improve the cognitive functions of AD patients, mainly including learning, memory and daily life capability [58]. In general, rTMS-COG seems to be a promising effective and safe treatment for AD [59-63].

Physical Activity and Intermittent Hypoxic Training

One of the most effective strategies to maintain physical and mental health is physical activity, which can promote brain plasticity, improve cognitive ability, and reduce the risk of cognitive decline [64-66]. Regular aerobic exercise can slow down the progress of AD in high risk population. In a middle-aged, at-risk cohort, a physically active lifestyle can decrease the key biomarkers of AD pathophysiology [67]. The researchers argue that physical activity and cognitive training may prevent recognition memory defects related to Aβ neurotoxicity [68,69]. Treadmill exercise ameliorates short-term memory by boosting neurogenesis in Aβ-induced AD rats model [70].

Oxygen is essential for maintaining the normal function of almost all organs, especially for the brain, which is one of the most oxygen consuming organs in the body. Exercise includes aerobic exercise and anaerobic exercise, mainly through the regulation of body metabolism, to stimulate the potential in the body. Moderate or intermittent hypoxic training is also an important means of against hypoxic injury intervention, which has been applied to improve endurance of athletes. In the course of Aβ-induced pathology metabolic dysfunction is an early and causative event [71]. It has been reported that adaptation to cyclic hypoxia can effectively prevent oxidative and nitrous stress, prevent neurodegeneration and protect cognitive function in experimental AD rats. [72,73] and they hypothesized that adaptation to induced hypoxia may prevent dementia, the protective mechanisms may be due to reducing oxidative stress and increasing the density of cerebral vascular network [74]. Our team found that moderate hypoxia (22.8-76 mmHg) can promote the proliferation of neural stem cells and enhance the differentiation of neural stem cells into the TH-positive neurons [75]. There is also epidemiological evidence for such effects, that is altitude of residence may impact the risk for dying of Alzheimer dementia [76]. There is a growing number of evidence that intermittent hypoxic training (IHT) can mobilize human potential and enhance cerebrovascular function, which is beneficial to hypertension, arrhythmia and mental stress [77].

Other Ways

To prevent and cure AD, in addition to the above-mentioned treatment methods, it also involves nutrition, music, social activities, etc. People who actively participate in social activities and play games have a relatively low risk of mild cognitive impairment [78]. Using a

computer, engaging in a higher number of mentally stimulating activities, is associated with a decreased risk of mild cognitive impairment among community-dwelling older persons [79]. The risk of dementia is associated with lifestyle, and good lifestyle implies a lower risk of dementia [80]. More than this, Nutrition can directly modulate susceptibility to AD [81]. Reduce trans fatty acids may contribute to the primary prevention of dementia [82]. Dietary salt promotes tau phosphorylation, which leads to cognitive impairment, a salt-rich diet can make nitric oxide decrease in brain endothelial cells and cerebral hypoperfusion reduction, resulting in cognitive impairment [83]. Modified Mediterranean-ketogenic diet modulates intestinal microorganisms and short-chain fatty acids in association with AD markers in patients with mild cognitive impairment [84]. Music intervention and chair-based exercise may improve significantly in quality of life in AD [85,86].

Conclusion

So far, no breakthrough has been made in drug development for AD, the progress of novel non-invasive brain stimulation methods has shown promise as a non-pharmacological treatment. Walking, light and their combination are effective therapies to improve sleep quality of AD patients [87]. TMS and tDCS can regulate nerve excitability in a non-invasive, painless and reversible way, making them potential valuable tools. Recently, a clinical trial of transcranial electromagnetic therapy for AD shows that it can enhance cognition and brain connection [88]. Nutrition may develop into one of the ways to prevent or even treat AD, especially if combined with other treatments, such as antidepressant intervention, brain exercise, physical exercise, etc [89]. Mediterranean diet and physical activity both can reduce the risk of AD [90]. As for IHT, it has also been reported that it has beneficial effects not only on AD but also on other neuropathy, including circulatory disorders, ischemic stroke. Therefore, it is necessary to further study the potential advantages of IHT in AD and its specific mechanism.

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