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REVIEW ARTICLE

Effect of Transcranial Pulse Stimulation for the Treatment of Alzheimer´s Disease and its Related Symptoms

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Abstract: Alzheimer's disease (AD) is the most common cause of neurodegenerative cognitive impairment. Brain stimulation techniques based on the delivery of transcranial shockwaves are currently being studied for their increasing popularity as an approach to modulate the human brain in a focal and targeted manner making this therapy a promising line of action against AD. In the present manuscript, we review for further understanding whether transcranial pulse stimulation (TPS) is a beneficial treatment for AD patients. PubMed, Google Scholar, and Cochrane databases were accessed with the search criteria set from year 2001 to 2022 and the following keywords were used: "transcranial pulse stimulation", "focused ultrasound", "noninvasive treatment and Alzheimer" and "TPS". The search was focused on papers that provide evidence on the biological bases of the method, as well as its safety and tolerability. Even though more studies are needed with greater scientific rigor, such as a double-blind and randomized study versus a placebo, TPS is an excellent and safe therapeutic option for AD. This novel approach accompanies currently available treatments and complements them, helping to maintain greater stability of the disease and slowing its progression. The biological effects and potential mechanisms of action of TPS for the improvement of cognitive function are further discussed.

Keywords: Alzheimer´s disease, dementia, mild cognitive impairment, neuromodulation, transcranial pulse stimulation, transcranial shockwaves.

1. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of neurodegenerative cognitive impairment, age being the main risk factor for developing Alzheimer's-type dementia. The exact causes triggering the onset of the disease remain currently unknown [1]. Nevertheless, it is general knowledge that AD is related to the deposition of beta-amyloid (Aβ) protein in the brain [2]. The protein deposition leads to the formation of tangles of phosphorylated Tau protein (pTAU) with loss of synapses and posterior brain atrophy [1, 2]. With the increase in life expectancy, it has been estimated that there are around 55 million people worldwide who suffer from this disease [3].

Currently, available treatments can alleviate symptoms and slow down the progression of the disease. Nevertheless, those treatments not only fail to cure the disease but are also insufficient when it comes to improving patients' functional capacity and quality of life, resulting in a burden for both the caregivers and the public health system [4]. Hence, there is a pressing need to find new therapeutic options to complement current therapies and improve the quality of life of patients and their families [1, 5].

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Transcranial pulse stimulation (TPS) is a non-invasive therapy that has been gaining interest in recent years with increasing supporting evidence and therefore, growing acceptance among the medical community [6]. TPS technique consists of repetitive single ultrashort pulses that stimulate different brain regions. By delivering the pulses guided with a neuronavigation device, TPS can target the human brain in a highly focused and precise manner. For this purpose, this technique uses mechano-acoustic pulses (shock waves) of low intensity (4Hz), and short duration (3us) that are repeated every 200-300ms. These physical, mechanical-acoustic shocks are received by the neurons and produce a series of favorable changes in the brain, both at the neural and the blood-brain barrier levels [7, 8]. Unlike the alternative two non-invasive brain stimulation techniques that have been traditionally used for dementia treatment, *i.e.,* transcranial direct current stimulation (tDCS) [9] and transcranial magnetic stimulation (TMS) [10], TPS is not based on the application of direct or induced electric current. This differentiating feature allows TPS to overcome the classic limitations of tDCS and TMS due to electrical conductivity problems [11], in addition to the inability of reaching deep brain areas [12]. Therefore, by using lower ultrasound frequencies TPS can successfully deliver good accuracy and spatial resolution to modulate subcortical regions [13]. For this reason, TPS represents a new concept in the treatment of cognitive impair-

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ment associated with neurodegenerative diseases. Moreover, TPS is a safe therapeutic option considering that no significant adverse effects have been yet described [14].

In the present manuscript, we perform a qualitative systematic review with the aim of further understanding whether TPS is beneficial for the treatment of AD patients. The biological effects and the TPS potential mechanisms of action for the improvement of cognitive function will also be discussed finally debating if this therapy is a promising alternative to conventional treatments against AD.

2. LITERATURE OVERVIEW

For this review, the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) criteria were used. Papers indexed in PubMed, Google Scholar and Cochrane databases 2001 to 2022 were searched and the following terms were used (in title/abstract): "transcranial pulse stimulation", "focused ultrasound", "non-invasive treatment and Alzheimer" and "TPS". Only manuscripts from peer-reviewed journals, written in English and published after 2001 were included. In total, of 84 hits, 75 articles were retrieved for detailed inspection and 5 met all inclusion criteria (see Fig. **1** for a detailed flow chart of study selection). Preclinical studies and studies referring to pathologies other than AD were not selected. Moreover, studies, where patients were not stimulated with TPS with the Neurolith® equipment, were excluded.

3. AVAILABLE EVIDENCE FOR TPS AS ALZHEIMER'S TREATMENT

Five articles met the inclusion criteria for the study and are summarized in Table **1**. In all of them, TPS was used as a novel add-on therapy for AD patients. The first work that followed up patients evaluating their cognitive performance [15], reported an improvement in cognitive functions. Thirty-five patients potentially with AD were included and were treated with the Neurolith® device. Participants underwent 3 sessions per week for 2-4 weeks (three patients for 2 weeks, one patient for 1 week and the rest for 4 weeks). The equipment was set to a frequency of 5Hz. The cognitive evaluation was performed with the CERAD score battery (Consortium to Establish a Registry for Alzheimer's Disease), observing significant improvement and stability in the three-month follow-up. Moreover, by using functional magnetic resonance (fMRI) the authors reported an increase in connectivity at the level of the hippocampus, parahippocampal, parietal and precuneal cortex. This improvement was confirmed/ratified in a subsequent study [16] where greater connectivity was observed in the stimulated areas (dorsolateral prefrontal cortex, memory, and language networks), against a deterioration compatible with the normal progression of the disease in unstimulated areas.

Cont *et al.* [17] evaluated 11 patients with mild, moderate, and severe stages of AD. The authors included patients with positive biomarkers or patients who had Alzheimer-like clinical syndrome. They examined their cognitive performance before and after the treatment, using the Alzheimer's Disease Assessment Scale (ADAS total) including ADAS cognitive score (ADAS Cog) and ADAS affective scores, Mini-Mental Status Examination (MMSE) and Montreal Cognitive Assessment (MoCA). For stimulation, TPS was set at a frequency of 4Hz, and the stimulation areas were the same as those treated by Bestiner *et al.* [15]. Some subjects underwent treatment on alternate days for two weeks with a total of 6,000 pulses received, while others received 3,000 pulses on consecutive days for 12 days. The authors observed an improvement mainly in global performance on the ADAS total score. Moreover, improvement was also reported in patient's subjective perception.

Novak and Lohse-Busch [18] performed the study with the longest follow-up of patients published up to date. For this study, 6 patients that had been treated with TPS for 10 years were followed-up. After 10 years the authors delivered a booster treatment consisting of 6 sessions performed for two weeks, as well as a monthly maintenance session. Two years after the initiation of the treatment, patients underwent intensive treatment again receiving 6 sessions over two weeks. The authors reported better cognitive performance of patients compared to the expected natural evolution of the

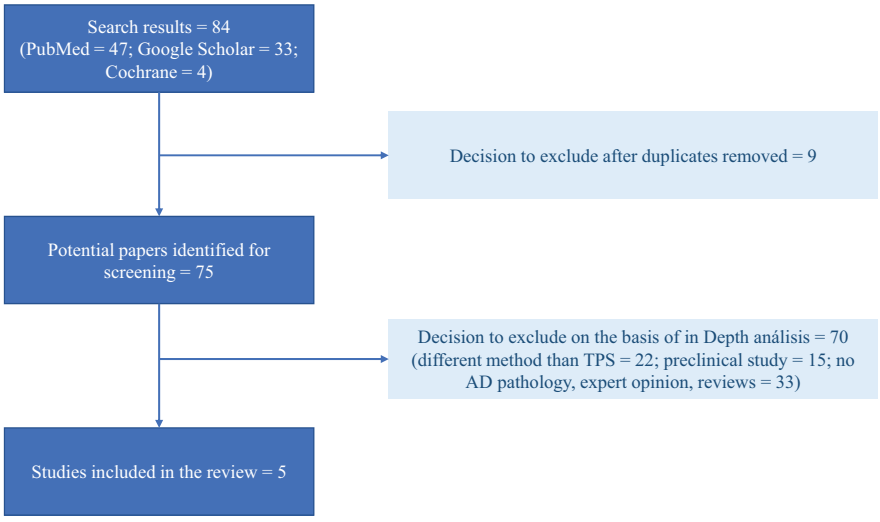

Fig. (1). Study selection process.

Table 1. Main characteristics of the reviewed manuscripts.

Manuscript	Year of Publication	Number of Patients	Methodology	TPS Conditions	Main Outcome	Follow-up	Major Findings
Dörl *et al.* [16]	2019	35	Prospective	-3 sessions per week every other day for 2-4 weeks with 6,000 pulses per session (5Hz)	-Cognition (CERAD)	Yes (3 months)	-Significant improvement and stability at 3-month follow-up in CERAD score -Increased connectivity in fMRI at the hippocampal level
Cont *et al.* [17]	2022	11	Retrospective	-3 sessions per week every other day for 2 weeks with 6,000 pulses per session (4 Hz) -12 ongoing sessions with 3,000 pulses (4Hz)	-Cognition (ADAS, MMSE, MoCA)	No	-TPS is safe and well tolerated -Global cognitive improvement in the Total ADAS score
Matt *et al.* [19]	2022	18	Prospective	-3 sessions per week every other day for 4 weeks with 6,000 pulses per session (5 Hz)	-Functional connectivity (fMRI)	No	-Increased connectivity in the stimulated areas (DLPF, memory and language networks) -High functional specificity of neuromodulation with TPS
Novak *et al.* [18].	2022	6	Prospective	-3 sessions per week every other day for 2 weeks with 6,000 total pulses (frequency not specified)	-Cognition (CERAD)	Yes (10 years)	-Clinical improvement compared to the expected normal progression -An annual booster treatment would maintain the benefits
Matt *et al.* [19]	2022	18	Prospective	-3 sessions per week every other day for 2-4 weeks with 6,000 pulses per session (5Hz)	-Depressive symptoms (BDI)	Yes (3 months)	-Decrease in depressive symptoms and improvement in BDI scores

disease. Although the cognitive decline progressed, this happened at a slower rate than naturally expected for those patients. The intensive treatment re-delivered two years later achieved a greater improvement with the monthly sessions, however, not being as significant as the first booster. The first booster achieved an improvement of 12.8 points on the CERAD score, achieving 4.5 points of improvement with the second booster. This suggests that patients could benefit from an annual booster treatment, considering that the progression curve showed patients to be stable for up to one year. This was evidenced by the slight decrease of 0.8 points in the CERAD score followed by a faster and more pronounced decline shown until the second year, when the second booster was administered. Hence, the annual booster may help maintain the initial benefit observed over longer periods of time. Nevertheless, benefits do not only extend to patient's cognitive performance improvement.

TPS treatment has also been shown to improve a patient´s mood and emotional state. In the study performed by Matt *et al.* [19], 18 patients potentially cursing with AD and depression were evaluated. Patients were treated with three weekly sessions for 4 weeks, except for three patients who were treated for two weeks, and one patient treated for three weeks. The frequency used was 5Hz and 6,000 pulses per session. The follow-up was performed after three months. Improvements in the Beck Depression Inventory (BDI) were observed with a significative decrease in BDI of 2.36 points.

4. SAFETY AND TOLERABILITY

It is key to highlight the wide-ranging safety of TPS. Adverse effects are infrequent and, when occurring they range as mild events. In the study that included the largest number of patients [15], 93% did not experience any adverse effects. Only 7% of the patients reported adverse events being the most frequent headaches that were naturally resolved. To a lesser extent, dizziness and paresthesia in the application area were also reported with spontaneous resolution. Other

described events were unpleasant feelings or pressure around the area of application [20].

5. TPS MECHANISM OF ACTION AND BIOLOGICAL EFFECTS

The present review evidences the safety and tolerability of TPS for patients with AD. This approach not only improves the patient´s cognitive performance and quality of life but also reduces depressive symptoms and apathy [19, 21], which are often more disabling than cognitive deficits. Our own experience as a clinical center using TPS over the last two years confirms the results observed in the reviewed studies. In a total of 36 patients treated in our clinic with a diagnosis of mild to moderate AD, we have demonstrated during the follow-up that TPS not only causes a stabilization of the clinical profile of our patients, but also a slight improvement in the emotional state and cognitive function, specifically in such important areas as temporal orientation and immediate episodic memory (preliminary results pending of publication).

The question that remains to be answered is the potential mechanism of action of TPS. In this review, we hypothesize that TPS could be acting on cognitive symptoms through several mechanisms (Fig. **2**). Firstly, low-frequency TPS has been reported to act on the microtubules by modifying their spatial conformation leading to an alteration in the interaction between neurons in a positive manner. Specifically, transcranial stimulation induces an expansion and contraction of microtubules that favors the formation of channels and fenestrae, improving communication between neurons and the passage of molecules [22]. Moreover, TPS also induces pore formation modifying the exchange between neurons as well as their plasticity [7]. This mechanical effect and its impact on the membrane's ion channels generates an opening of the blood-brain barrier, optimizing the passage and transport of immune factors [8]. Nevertheless, TPS does not solely act on neurons, it has also been demonstrated to modify the blood-brain barrier by increasing the permeability and thus improving lymphatic drainage [22], in addition to allowing the access of immune cells and stimulating neovascularization. Therefore, it has been proposed that vascular defects can precede the onset of other AD hallmarks features, becoming an important event that leads to neuronal cell death and dementia [23].

The increased vascularization and angiogenesis promoted by TPS could improve cerebral blood flow and secondarily benefit neuroplasticity. Preclinical studies have revealed increased levels of anti-amyloid beta protein antibodies with

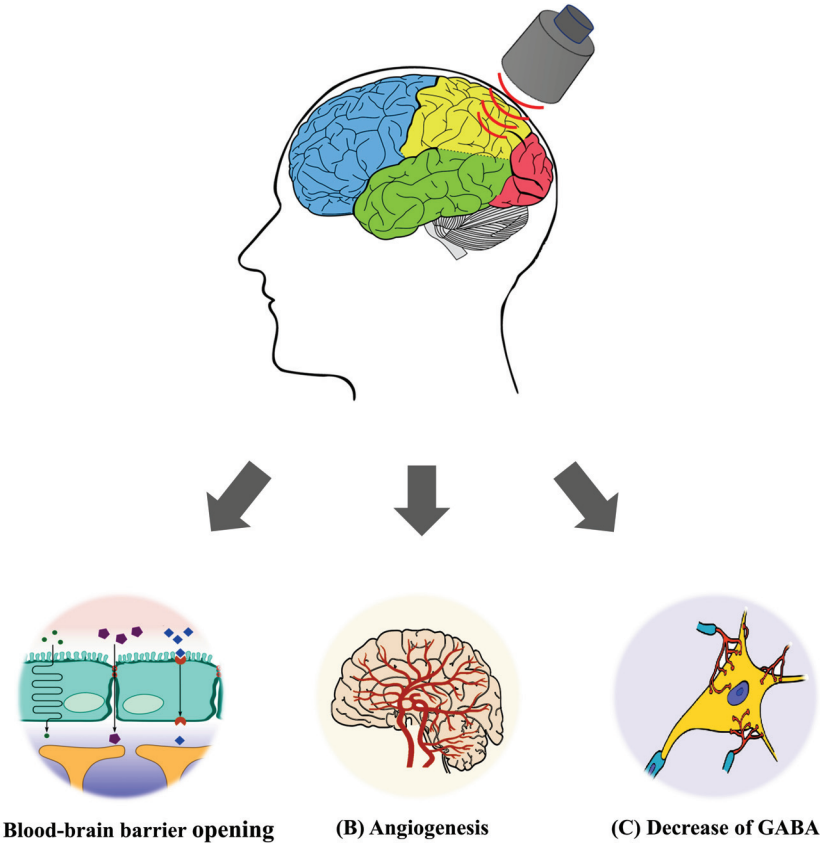

Fig. (2). Potential mechanisms of action of transcranial pulse stimulation.
Note: The figure shows three potential mechanisms of action of transcranial pulse stimulation in the treatment of patients with Alzheimer's disease: (**A**) opening of the blood-brain barrier; (**B**) promotion of angiogenesis; (**C**) decrease in GABA concentration. Fig. **A**: adapted from "Blood-brain barrier transport" by Kuebi = Armin Kübelbeck licensed under CC BY 3.0. To view a copy of this license, visit https://creativecommons.org/licenses/by/3.0/?ref=openverse. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

the consequent reduction of cerebral amyloid plaques [24]. The benefits of this treatment also include cell proliferation and atrophy reduction as demonstrated by the work performed with cell cultures [25]. TPS has also been proven to trigger microglia activation through increased protein expression, without generating cell recruitment or inflammation [26]. Preclinical studies have found that activation of microglia could lead to a more efficient brain functioning with a subsequent reduction of Aβ plaques through lysosomes [27, 28], in addition to cell proliferation [25]. As a result, this could produce a reduction of brain atrophy in patients as demonstrated by a study performed with 17 patients with AD that found an improvement in cognitive performance and cortical thickness [29]. This could be achieved by an increased protein expression with the following activation of microglia, without triggering cell recruitment or inflammation [26].

Finally, the stimulation received by the brain neurons leads to an increased metabolism, stimulation of vascularization and favorable changes in neurotransmitter levels. Specifically, a decrease in GABA levels has been found together with increased serotonin and dopamine levels as well as an elevation of growth factors such as brain derived growth factor (BDNF), vascular-endothelial growth factor (VEGF) and nitric oxide [7, 8, 30]. While Aβ plaques are likely to cause the initial damage associated with AD, it has been largely hypothesized that the final neurodegeneration may be the result of prolonged exposure to the GABA neurotransmitter that is released when the brain is injured or diseased [31]. In normal conditions, GABA is the main inhibitory neurotransmitter that plays an important role by slowing down neuronal excitatory activity in response to certain situations. When the brain is injured due to a traumatic injury, a stroke, or the accumulation of toxic proteins as in AD, the GABAergic system activates a response to repair the brain mechanisms. This essentially involves a chain of neurochemical processes designed to prevent further damage. As part of this chain, reactive astrocytes accumulate and produce GABA at the injury site. Thus, GABA may play a neuroprotective role by reducing inflammation. However, when GABA release is extended over time it can have a detrimental long-term impact by suppressing normal neuronal activity [32]. Elevated levels of GABA in the dentate gyrus have been demonstrated to inhibit normal learning and memory while reduced levels allow to improve the excitatory/inhibitory balance in the brain, increasing neuronal activity and memory functioning in mice models of AD [32].

Regarding the limitations of this work, we found that in the available scientific evidence, the research protocols were heterogeneous in terms of the stimulation of brain regions, duration of the stimulation and frequency in which the equipment was used, as well as in the assessment scales conducted. It should also be noted that further studies using TPS for the treatment of AD are needed, with greater scientific rigor such as a double-blind and randomized study versus placebo.

CONCLUSION

Based on the available evidence and our own experience, TPS is an excellent and safe therapeutic option for AD that accompanies currently available treatments and complements them helping to stabilize or slow down the progression of the disease. Treatment with TPS also produces significant improvements in the cognition and emotional/behavioral sphere, as well as in the quality of life of patients and families. Overall, TPS represents a promising line of research that raises the chances of patients to achieve clinical improvement together with a better prognosis.

LIST OF ABBREVIATIONS

Aβ	=	Beta-Amyloid
AD	=	Alzheimer's Disease
ADAS	=	Alzheimer's Disease Assessment Scale
CERAD	=	Consortium to Establish a Registry for Alzheimer's Disease
MMSE	=	Mini-Mental Status Examination
MoCA	=	Montreal Cognitive Assessment
TPS	=	Transcranial Pulse Stimulation
tDCS	=	Transcranial Direct Current Stimulation
TMS	=	Transcranial Magnetic Stimulation

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

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