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Non-invasive sound wave brain stimulation with Transcranial Pulse Stimulation (TPS) improves neuropsychiatric symptoms in Alzheimer's disease

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ABSTRACT

Background: This study explores Transcranial Pulse Stimulation (TPS) as a potential non-invasive treatment for Alzheimer's disease (AD), focusing on its impact on cognitive functions and behavioral symptoms.

Methods: In a prospective, one-arm open-label trial, ten patients with mild to moderate dementia due to AD were assessed using the Alzheimer's Disease Assessment Scale (ADAS-Cog), Neuropsychiatric Inventory (NPI), Pfeffer Functional Activities Questionnaire, and Zarit Caregiver Burden Interview. Assessments occurred at 30- and 90-days post-treatment. The TPS protocol consisted of 10 sessions over five weeks, using the Neurolith® device to deliver 6000 focused shockwave pulses at 0.25 mJ/mm2 and a frequency of 4 Hz.

Results: TPS significantly reduced neuropsychiatric symptoms, with NPI scores decreasing by 23.9 points (95% CI: −39.19 to −8.61, p = 0.0042) after 30 days, and by 18.9 points (95% CI: −33.49 to −2.91, p = 0.022) after 90 days. These changes had large effect sizes (Cohen's dz = 1.43 and dz = 0.94, respectively). A decreasing trend was observed in the ADAS-Cog score (−3.6, 95% CI: −7.18 to 0.00, p = 0.05) after 90 days, indicating a potential reduction in cognitive impairment, though not statistically significant.

Conclusion: The preliminary results indicate that TPS treatment leads to significant improvement in neuropsychiatric symptoms in AD patients, showing promise as a therapeutic approach for AD. Further research is needed to fully establish its effectiveness, especially concerning cognitive functions.

Dear Editor,

Alzheimer's disease, a dominant cause of dementia globally, is escalating in prevalence, with an estimated 50 million individuals currently affected. The economic and social burdens of this condition are significant, with costs expected to soar. AD typically manifests with episodic memory decline, progressing to a broader cognitive impairment, severely impacting daily living activities. Pharmacological treatments have been limited to symptomatic relief, with recent drugs like aducanumab and lecanemab showing mixed results regarding efficacy and safety.

In our research we investigate Transcranial Pulse Stimulation (TPS) as a promising non-invasive intervention for AD [1–8]. TPS employs focused sound wave pulses through the skull, targeting deep brain structures involved in cognitive and neuropsychiatric functions. This study, an open-label trial, enrolled ten patients with mild to moderate dementia due to AD (baseline characteristics are reported in supplementary material 1). The intervention protocol comprised 10 TPS sessions over five weeks, using Neurolith® to deliver focused shockwave pulses. Key outcome measures included the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and Neuropsychiatric Inventory (NPI) [9], supplemented by functional scales like the Pfeffer Functional Activities Questionnaire and the Zarit Caregiver Burden Interview. The detailed description of our methods is presented in the Supplementary material 2.

Our results demonstrate a significant impact of TPS on neuropsychiatric symptoms. The NPI scores, which evaluate 12 neuropsychiatric domains including delusions, hallucinations, agitation, and depression, showed a marked improvement (Supplementary material 3). At 30 days post-treatment, we observed a mean reduction of 23.9 points (95% CI: −39.19 to −8.61, p = 0.0042), and at 90 days, the reduction was 18.9 points (95% CI: −33.49 to −2.91, p = 0.022). These reductions signify large effect sizes (Cohen's dz = 1.43 at 30 days and dz = 0.94 at 90 days) and are clinically relevant, indicating a substantial decrease in the severity and frequency of neuropsychiatric symptoms in AD patients (Fig. 1).

Regarding cognitive functions assessed by ADAS-Cog, which covers memory, language, praxis, attention, and other cognitive abilities, our study noted a trend towards improvement. Although the change in ADAS-Cog scores did not reach statistical significance, there was a noticeable reduction in scores from baseline to 90 days post-treatment (mean difference of −3.6, 95% CI: −7.18 to 0.00, p = 0.05). This trend suggests a potential cognitive benefit of TPS in AD, warranting further investigation in larger and more extended trials (Fig. 1).

The mechanism behind TPS's efficacy is thought to involve cavitation, leading to mechanosensing and mechanotransduction at the cellular level. This process translates mechanical forces into biological responses, including enhanced blood flow, neoangiogenesis, and anti-inflammatory action, potentially contributing to the improvements in neuropsychiatric symptoms. Furthermore, TPS is hypothesized to stimulate brain-derived neurotrophic factor production [10] and improve glymphatic clearance, facilitating the removal of neurotoxic proteins such as beta-amyloid.

Our study, albeit limited by its open-label design and small sample size, marks a significant step in exploring TPS as a treatment modality

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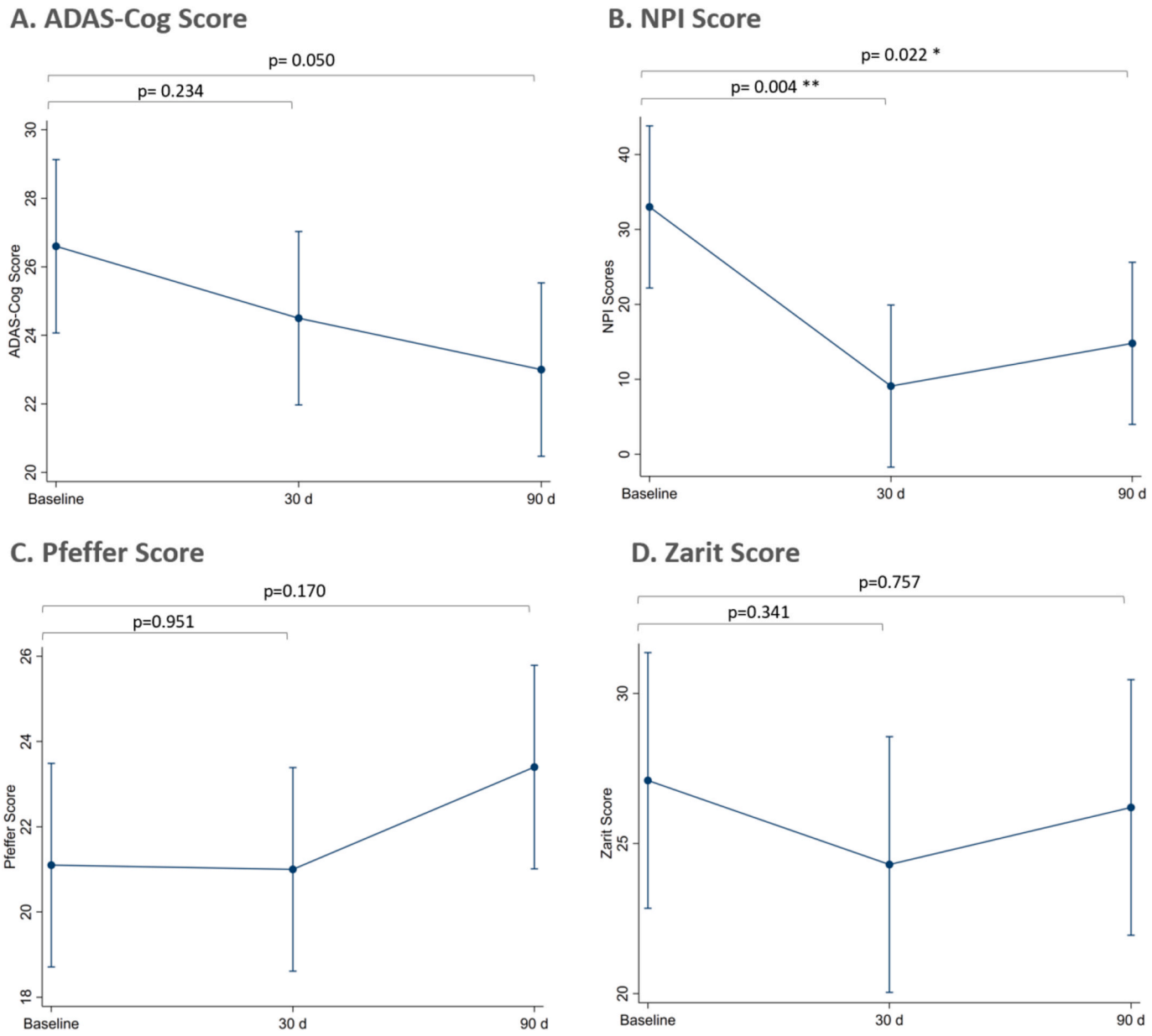

Fig. 1. Longitudinal changes after TPS at 30 and 90 days. Means with 95% CIs.

for AD. The improvements in neuropsychiatric symptoms are particularly noteworthy, addressing a critical aspect of AD management. The observed trend in cognitive function enhancement further positions TPS as a promising therapeutic avenue in AD.

In conclusion, TPS represents a groundbreaking approach in the treatment of Alzheimer's disease, particularly in alleviating neuropsychiatric symptoms. The potential cognitive benefits of TPS, indicated by the trend in ADAS-Cog score improvements, open new avenues for research and offer hope for a condition that has long been challenging to treat. We advocate for larger, randomized controlled trials to validate these findings and explore the long-term efficacy and safety of TPS in AD.

CRediT authorship contribution statement

Gilson Tanaka Shinzato: Conceptualization, Data curation, Investigation, Writing – original draft. **Tatiane Assone:** Conceptualization, Data curation, Investigation, Project administration, Writing – original draft. **Paulo C. Sandler:** Investigation, Writing – original draft. **Kevin Pacheco-Barrios:** Conceptualization, Data curation, Formal analysis, Writing – original draft. **Felipe Fregni:** Conceptualization, Supervision, Writing – review & editing. **Marcia Radanovic:** Investigation, Project administration, Writing – original draft. **Orestes Vicente Forlenza:** Investigation, Project administration, Writing – original draft. **Linamara Rizzo Battistella:** Conceptualization, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.03.007.

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