Optimizing Clinical Outcomes in Transcranial Pulse Stimulation

Toward a Standardized Multidimensional Framework in Neurodegenerative Diseases

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BACKGROUND

Transcranial Pulse Stimulation (TPS) is an emerging non-invasive neuromodulation technology based on focused ultrasound capable of delivering highly precise mechanical stimulation to cortical and subcortical brain networks. Over the past decade, growing clinical evidence has supported its safety and therapeutic potential in neurodegenerative disorders, particularly Alzheimer's disease, with preliminary applications extending to Parkinson's disease and other cognitive disorders. Published studies have reported improvements in cognition, mood, neuropsychiatric symptoms, and functional brain connectivity, suggesting that TPS may influence large-scale neural networks involved in memory, executive function, and behavioral regulation. Despite these encouraging findings, the field remains limited by considerable heterogeneity in treatment protocols, patient selection, and outcome assessment methodologies, making cross-study comparisons difficult and hindering the development of evidence-based clinical standards.



OBJECTIVE

To critically analyze the outcome measures currently employed in TPS research, identify methodological limitations affecting the interpretation of clinical efficacy, and propose a standardized multidimensional framework capable of improving the evaluation of therapeutic response in Alzheimer's disease, Parkinson's disease, and related neurodegenerative conditions.

METHODS

A narrative review of the available TPS literature was performed, outcome measures. In addition, a real-time expert survey strategy focusing on cognitive, neuropsychiatric, functional, neurophysiological, and neuroimaging outcomes reported in clinical studies. Particular attention was given to the variability of assessment tools, follow-up schedules, and patient populations. Based on the identified limitations, a structured framework was developed integrating traditional clinical scales, emerging clinical biomarkers, and patient-centered is proposed as a mechanism for developing international consensus regarding outcome prioritization and standardization within the TPS community.

RESULTS

Current evidence consistently demonstrates a favorable safety profile and promising efficacy signals for TPS. Improvements have been reported across multiple cognitive domains using instruments such as CERAD, ADAS-Cog, and MoCA, while reductions in depressive and neuropsychiatric symptoms have been observed through validated behavioral assessments. Neuroimaging studies have further demonstrated increased functional connectivity within networks associated with memory and executive processing, supporting a biologically plausible mechanism of action. However, substantial variability exists regarding the choice of endpoints, timing of assessments, treatment protocols, and definitions of clinical response. This heterogeneity limits reproducibility and complicates comparisons among studies. Furthermore, traditional outcome measures may not adequately capture the multidimensional effects of network-level neuromodulation. To address this gap, we propose the incorporation of a structured clinical biomarker panel encompassing: (1) dynamic cognitive performance measures, including processing speed and working memory; (2) behavioral indicators such as apathy, initiative, and social engagement; (3) functional performance metrics including dual-task execution and real-world activity performance; (4) language-based markers such as verbal fluency and response latency; (5) motor parameters relevant to Parkinson's disease; and (6) digital biomarkers derived from continuous monitoring of daily activity, mobility, and sleep patterns.

DISCUSSION

The future development of TPS research requires a transition from heterogeneous outcome reporting toward a standardized and internationally accepted Core Outcome Set. We propose a multidimensional framework integrating traditional clinical measures, emerging clinical biomarkers, and expert consensus methodologies to improve sensitivity, reproducibility, and clinical relevance. Such an approach may facilitate multicenter collaboration, strengthen evidence generation, and accelerate the integration of TPS into the therapeutic landscape of Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders.

CONCLUSION

The therapeutic effects of TPS appear to extend beyond isolated cognitive improvements and likely reflect broader modulation of interconnected neural networks. Consequently, reliance on conventional cognitive scales alone may underestimate the true clinical impact of treatment. A multidimensional assessment strategy integrating cognitive, neuropsychiatric, functional, behavioral, and digital domains may provide a more sensitive and ecologically valid representation of patient response. Emerging evidence also suggests that treatment outcomes may be influenced by factors such as age, disease stage, baseline cognitive reserve, and neuropsychiatric profile, emphasizing the importance of patient stratification and personalized therapeutic approaches.

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