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Protocol for a living systematic review of randomised controlled trials on the clinical efficacy of transcranial pulse stimulation in neurological and psychiatric conditions

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ABSTRACT

Introduction Transcranial pulse stimulation (TPS) is a novel technology with therapeutic promise for Alzheimer's disease. Given its novelty and the rapidly evolving research in neurology and mental health using this technology, large randomised controlled trials are expected. Therefore, an independent and up-to-date synthesis of the available evidence is needed. In our effort to create a living systematic review of the clinical efficacy of TPS across various conditions, we aim to describe its methodology to ensure its transparency and scientific rigour. This protocol details the predefined methods related to search frequencies, updates to the review and quantitative synthesis.

Methods and analysis We will only include randomised controlled trials involving clinically diagnosed populations and comparing active TPS to sham TPS. We will search MEDLINE, CENTRAL and Web of Science, as well as trial registries and grey literature. The principal searches in databases and trial registries will be rerun monthly, and new evidence will be integrated. Study selection, data extraction and risk-of-bias assessments will be performed independently and in duplicate. All relevant clinical outcomes measured with validated psychometric scales and tests will be collected. The relevance of a quantitative synthesis, the studies to be included in pairwise meta-analysis, appropriate scales, questionnaires and time points will be discussed by the research team annually. If a meta-analysis is conducted, we will use the standardised mean difference as the measure of effect size. We will assess our confidence in the cumulative evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Ethics and dissemination For this systematic review and meta-analysis, we will collect existing data without generating new datasets. Therefore, ethics approval or consent to participate is not required.

We will publish our initial systematic review when a total of four randomised controlled trials across different health conditions using active TPS compared with sham TPS are available. At this stage of our project, we anticipate updating the living systematic review annually following the publication of the baseline review. We will conclude the living phase of the review when high certainty of evidence is achieved or if the topic loses its relevance.

Systematic review registration CRD42024595947.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Transcranial pulse stimulation (TPS) is a novel neuromodulation technology, and future randomised controlled trials are expected.
⇒ We aim to summarise and regularly update the available evidence from studies using TPS in mental health and neurological conditions.
⇒ This protocol is intended to transparently document the methodology and to prespecify the procedures and decision-making processes for the quantitative synthesis.
⇒ Limitations are anticipated due to heterogeneous protocols, which may limit the relevance of the quantitative synthesis.

INTRODUCTION

In 2019, the first report on transcranial pulse stimulation (TPS), a new paradigm in the field of neuromodulation, was published in *Advanced Science*.[1] This report introduced TPS as a novel technology involving the transcranial application of ultrashort microsecond range ultrasound pulses targeting both cortical and deeper brain structures.[2]

TPS is presented as a promising treatment for Alzheimer's disease. It has held a European Commission marking (*Conformité Européenne* (CE) marking) for this indication since 2018, and it appears to show consistent short-term improvements in cognition and mood in participants with Alzheimer's disease.[3–9] It is hypothesised that TPS efficacy is mediated by the activation of mechanosensitive membrane ion channels and receptors in the central nervous system.[2] EEG studies

indicate that TPS may reduce EEG entropy, suggesting a potential global reset of uncoordinated pathological neural activity. Functional MRI studies further suggest increased global efficiency in the cortical sensorimotor network.[3 10–12]

Since the initial observations of TPS efficacy in Alzheimer's disease, its potential for other conditions has also been explored. Significant effects have been reported in major depressive disorder, Parkinson's disease, mild cognitive impairment and attention deficit hyperactivity disorder (ADHD).[13–17]

Studies conducted on animal models show no brain damage even at energy levels 150 times higher than those permitted in humans.[1] No serious adverse effects have been reported in cohorts of healthy participants or in clinical studies. The adverse effects associated with transcranial ultrasound stimulation are similar to those of other neuromodulation techniques; they are mild to moderate in intensity and transient.[18–20] These include headaches, a feeling of pressure at the stimulation site, a sensation of heat, anxiety, discomfort, attentional difficulties, nausea, drowsiness and fatigue, and they occur in both active and placebo conditions. However, unlike repeated transcranial magnetic stimulation, TPS does not appear to induce seizure activity.

While preliminary data on the efficacy and safety of TPS are promising, the current evidence remains limited, notably because there is still a lack of randomised sham-controlled double-blind studies. Given the novelty of TPS and the rapidly evolving research on this intervention in neurological and psychiatric conditions, additional large randomised controlled trials (RCTs) are anticipated. In this context, an independent, up-to-date and continuously updated synthesis of the available evidence is needed. The aim of the present study is therefore to develop a living systematic review (LSR) of the clinical efficacy of TPS across conditions, with regular systematic searches and incorporation of newly published RCTs over time. At this stage of the LSR protocol, we aim to ensure transparency and scientific rigour by detailing our predefined methods for search frequencies, review updates and the rationale for potential choices regarding quantitative synthesis.

Our LSR, with the repeated incorporation of new evidence as it becomes available, will aim to determine whether active TPS is a safe and effective treatment compared with sham TPS across clinical conditions.

METHODS

Our methodology follows the Cochrane Collaboration's recommendations for conducting LSRs.[21] We adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines to ensure that this protocol contains all the recommended information.[22] The coordinator of this LSR (AD) is trained in advanced meta-analysis methods and has experience in conducting bibliographic research. The LSR is scheduled to begin on 1 September 2026.

Eligibility criteria

Type of studies

In our evaluation of clinical efficacy, we will include only RCTs. All other types of studies will be excluded to avoid the bias associated with non-randomised and non-controlled designs. We will include studies published from 2019 onwards, as this marks the first report of TPS in the scientific literature.[1] Articles in all languages will be considered.

Population

The clinical population will include individuals participating in a clinical study after a thorough diagnosis of a specific and well-defined health condition. All well-defined neurological and psychiatric disorders will be eligible. Studies focusing exclusively on isolated symptoms, without reference to a formally diagnosed condition, will be excluded. Studies involving healthy individuals will also be excluded.

Intervention and comparator

In the included studies, active TPS must be compared with sham TPS. Any type of TPS protocol will be included regardless of the neuromodulation parameters (eg, session duration and frequency, targets of interest). Sham TPS sessions must closely mimic the appearance and experience of active TPS sessions.

Outcomes and prioritisation

All relevant clinical outcomes will be collected using validated psychometric scales and tests.

We have defined cognitive and mood improvements as the two primary criteria for our LSR. This choice was made based on the expectation that TPS will primarily be studied in Alzheimer's disease, where cognitive decline and depressive symptoms are common, and because the impact of TPS on these outcomes has been described in preliminary studies.

We expect investigators to use validated and standardised cognitive scales such as the Montreal Cognitive Assessment or the Mini-Mental State Examination.[23 24] Additionally, data from condition-specific scales will also be collected. For instance, in Alzheimer's disease, scales such as the Consortium to Establish a Registry for Alzheimer's Disease test battery and the cognitive subscale of the Alzheimer's Disease Assessment Scale may be used.[25 26] We will also gather data from validated psychometric tests assessing various aspects of executive function, as well as neuroimaging and electrophysiology data.

For studies in other conditions, such as ADHD, we will include data from all validated psychometric scales used. Additional outcomes, such as quality of life and caregiver burden, will also be collected if they are measured with validated scales and questionnaires.

We will also collect data on adverse effects and the acceptability of TPS. This data will be descriptive and will provide information to better establish the risk-benefit ratio of TPS.

As the precise mechanisms of action of TPS remain incompletely understood, we will also collect all translational and mechanistic data reported in the included trials.

Search methods

We will conduct our searches in MEDLINE, CENTRAL and Web of Science. Embase is not currently available through our institutional library. Additionally, we will search trial registries, including the International Clinical Trials Registry Platform and ClinicalTrials.gov. To include data from grey literature, we will also search for unpublished dissertations and conference proceedings from key neuromodulation conferences, such as the International Brain Stimulation Conference and the European Conference on Brain Stimulation in Mental Health.

An experienced team member developed our MEDLINE search strategy, which will be pilot-tested and peer-reviewed by team members. A draft of search strategy for all sources is available in the online supplemental file 1. A highly sensitive Cochrane filter for RCTs was adapted and applied to the search strategies where appropriate; no other filters were used.

Given the novelty of this topic, we are aware that our search strategy may become outdated as new terms emerge. Therefore, we will evaluate the need to review and update our search methods and strategies annually during the November–December period to align with Medical Subject Headings term updates.

The primary searches in databases and trial registries will be conducted monthly. We will set up auto-alerts where possible to receive monthly reports on the available evidence. Each year, we will also search for conference proceedings from key neuromodulation conferences. Additionally, we will contact the authors of ongoing trials to enquire if new data will be available soon or if they are willing to share unpublished data. For each newly included trial, we will reach out to the corresponding author to ask for recommendations regarding any other relevant studies that should be considered for inclusion. We will also perform manual reference searches in newly included trials.

We anticipate that our initial search will yield a relatively small number of results due to the novelty of the topic. Therefore, we will not use any machine learning tools to handle the data initially. However, if the volume of data increases significantly during the living phase of our systematic review, we will revise our methodology to incorporate automation for data processing.

Data management and study selection

All search results will be managed using Zotero reference management software.[27] Duplicate entries will be semiautomatically removed. The remaining entries will then be uploaded into Rayyan, an automation tool for systematic reviews that allows for independent study selection based on titles and abstracts, followed by full-text review.[28]

The study eligibility form is available in the online supplemental file 2. Two raters will independently and blindly assess titles and abstracts using the form to exclude clearly irrelevant entries. Disagreements will be resolved through discussion, involving a third rater if necessary. Following this initial selection round, the full texts of the included articles will be assessed. This second selection round will also be conducted by two authors independently and in blind mode. Any disagreements will be resolved through discussion with a third author. For each entry excluded at this stage, we will specify the reasons for exclusion.

During the living phase of the review, two authors will rerun the searches monthly and independently screen newly identified records based on titles and abstracts. Full texts will then be assessed for all records retained at the first stage of screening. Any discrepancies will be resolved through discussion.

Data collection

The data extraction form was drafted by the first author (AD) and peer-reviewed by the research team. It includes study identification details (first author, year of publication), population characteristics (eg, sample size at baseline, percentage female, age, condition), TPS session details (eg, frequency, duration, targets) and sham TPS characteristics. It also includes a results section for outcomes of interest, the scales and questionnaires used, time points and corresponding sample sizes, means and SDs. We will also gather data on the availability of preregistered trial protocols, funding sources and potential conflicts of interest. The extraction form is available in the online supplemental file 2.

The data extraction form will be pilot-tested on the first three selected trials and adjusted if necessary. Two authors will independently extract data. If any data or relevant information is missing, we will contact the corresponding authors using their institutional email addresses, making up to three attempts over 1 month. Disagreements in the extracted data will be resolved through discussion with a third author.

In the case of multiple reports of a single trial, two authors will independently and blindly compare the trial characteristics, and only one report will be included. For crossover studies, we will use only the data collected before the crossover. If a study investigates more than one control condition, only the data from the sham TPS condition will be used. If different TPS modalities are compared within a single trial, we will combine the results from different intervention arms for comparison with sham TPS.

Whenever new evidence is identified through monthly searches, data extraction will follow the same protocol, with two authors independently and in duplicate.

Risk of bias

Risk of bias assessment will be performed at the outcome level. We will use the revised Cochrane risk-of-bias tool

for RCTs, which evaluates randomisation, deviations from the protocol, handling of missing data, outcome measurement and selective reporting.[29] Each domain will be classified as 'High' risk, 'Low' risk or 'Some concerns' based on the guidance questions incorporated in the tool. Two authors will independently conduct this evaluation, and in case of discrepancies, a third author will be involved to resolve conflicts through discussion.

If a quantitative synthesis is conducted, the risk of bias evaluation for each study at the outcome level will be presented in the forest plots.

We will critically analyse the results of the risk of bias assessment and discuss their impact on the robustness and validity of the review findings. As new evidence becomes available, the same risk of bias evaluation methods will be applied.

Patient and public involvement

Patients and members of the public will not be involved in the initial stages of this LSR. However, once sufficient evidence is available to inform potential recommendations for the clinical use of TPS, patient and public input will be sought to inform the design of future studies and to address issues related to the acceptability and feasibility of TPS from a patient perspective.

DISCUSSION

Synthesis methods

The research team will assess the feasibility of a quantitative synthesis for the included trials annually. During the early phase of our LSR, we expect only a limited number of RCTs to be published. It is also likely that these RCTs will investigate the efficacy of TPS in diverse conditions and settings, leading to significant clinical and statistical heterogeneity between studies. Clinical heterogeneity will be assessed through evaluation of clinical, technical and methodological differences between studies, and this evaluation will involve discussions with the entire research team. In case of substantial differences between the trials, only a narrative synthesis will be performed. In this case, the results of individual trials and the overall findings of the review will be presented using both text and table formats.

The included population will be described by presenting sociodemographic and diagnostic information. Details of TPS modalities will also be thoroughly described. Outcome data will be presented by time points, ranging from post-treatment to multiple-month follow-up.

The research team will discuss the relevance of a quantitative synthesis, the studies to be included in a pairwise meta-analysis and the appropriate scales, questionnaires and time points on an annual basis. If a meta-analysis is conducted, the standardised mean difference will be used as the measure of effect size. All analyses will be performed in R using the *meta* package.[30]

We will use inverse variance and random effects models due to the anticipated variability between studies. Sensitivity analyses will be conducted by comparing the results from random and fixed effects models. Sample size estimates will be presented using Cohen's d, which is interpreted as large if d=0.8, medium if d=0.5 and small if d=0.2.[31]

Statistical heterogeneity will be explored using inconsistency measures such as the χ^2 test (with significant heterogeneity indicated if $p<0.1$) and the I^2 statistic. The I^2 statistic reflects 'the percentage of total variation across studies that is due to heterogeneity rather than chance'. It ranges from 0% to 100%, with higher percentages indicating greater heterogeneity among studies. If I^2 exceeds 50%, we will investigate this heterogeneity using subgroup analyses and meta-regression, if appropriate, incorporating variables such as patient age, sex and baseline cognitive status as covariates.

Meta-biases

We will gather all prepublished protocols and statistical plans to identify selective reporting biases and post hoc decisions. We will also assess potential publication bias related to the effect of small positive trials using a funnel plot. In the results section of our published LSR, we will interpret our findings in the context of our meta-bias evaluation.

Confidence in cumulative evidence

We will assess our confidence in the cumulative evidence using the GRADE approach in GRADEPro[32]. Two authors will independently evaluate the risk of bias across studies, inconsistency, indirectness of the effect, imprecision in the results and the presence of publication bias in blind mode. In case of disagreement, a third author will be consulted to reach a consensus. Each time new evidence is incorporated into the synthesis, the GRADE evaluation will be updated accordingly.

Ethics and dissemination

For this systematic review and meta-analysis, we will collect existing data without generating new datasets. Therefore, ethics approval or consent to participate is not required.

We will publish our initial systematic review once a total of four RCTs across different health conditions using active TPS compared with sham TPS have been published. Our findings will be communicated in an international peer-reviewed journal. The living phase of the LSR will conclude when we achieve a high level of certainty in the evidence or if the topic loses its relevance. The methods, scope and necessity to maintain the systematic review as a living review will be reviewed annually, coinciding with the evaluation of the search strategy. Each year, we will review the newly available evidence and consider publishing an update to our LSR that incorporates the most recent findings. At this stage of our LSR project, we anticipate updating the LSR annually following the publication of the baseline review.

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