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Transcranial Pulse Stimulation for Alzheimer's Patients

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Abstract

Transcranial pulse stimulation (TPS) is a noninvasive neuromodulation therapy with Conformité Européenne (CE) marking for the treatment of Alzheimer's disease (AD). Initial pilot studies have demonstrated promising effects on cognitive function. This article focuses on the procedure for treating patients with AD using an MRI-guided, neuro-navigated TPS device. The protocol to be followed for this is described in detail, including the necessary procedures and device settings. A brief overview of the representative clinical results published to date is also provided. In addition to significant clinical improvements in cognition and affect, adverse events (AE) and possible adverse device events (ADE) are presented to provide safety data. Finally, the method is critically discussed. In the future, randomized controlled trials should be conducted to rule out any placebo effects. There is also currently a lack of long-term studies with a larger number of patients. Despite these unresolved questions, TPS has the potential as an adjunct treatment for Alzheimer's patients when used in a controlled, scientifically guided setting.

Introduction

Noninvasive brain stimulation (NiBS) techniques have become a focus of growing interest in dementia research, offering potential therapeutic strategies to mitigate cognitive and functional deficits associated with neurodegenerative diseases. Accumulating evidence suggests that NiBS could enhance cognitive function or slow cognitive decline in individuals with Alzheimer's disease (AD) across various stages of the condition[1,2]. Among these techniques, Transcranial Pulse Stimulation (TPS) is particularly notable for its ability to deliver highly focused and precisely targeted brain stimulation, not only on the cortical surface but also in deeper brain regions[3,4]. Side effects associated with TPS are rare, moderate in severity, and transient[3,5].

Initially developed in the fields of orthopedics and cardiology, therapeutic ultrasound therapy and extracorporeal shockwave therapy (ESWT) have been shown to promote tissue healing and improve blood flow. In orthopedics, ESWT was particularly applied to treat musculoskeletal

conditions such as tendinopathies and bone healing issues, while in cardiology, it was explored for its effects on vascular health[6,7]. TPS has been adapted for neurological applications, particularly in Alzheimer's research, showing promise in addressing cognitive decline and functional impairments[8,3,4]. This technique uses shockwaves to alleviate the symptoms of patients with Alzheimer´s disease, as demonstrated by pilot data from the working group of this tutorial[5]. Shock waves differ from ultrasound waves in that they do not involve a high-frequency alternating load[9]. The shock wave profile generated, as shown in **Figure 1**, clearly illustrates the singular pressure pulse and the subsequent flattening of the amplitude during TPS, along with the higher-frequency amplitude characteristic of ultrasound. Due to the high-frequency alternating stress, the energy of the ultrasound waves is absorbed by the tissue, which can lead to tissue warming-an effect not observed with shock waves. In other applications, high-energy shock waves are used, whereas in TPS, the energy introduced into the tissue is low-energy[9]. The potential effects on Alzheimer's disease were first reported as improvements in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[3], as well as increased cortical thickness in several areas[10] and changes in MR-network connectivity[11].

The mechanisms of action of TPS are currently under investigation, with research focusing on how this non-invasive technique modulates brain activity at the cellular level, potentially triggering mechanotransduction processes that could enhance neuroplasticity and improve cognitive function[3,4]. In shock wave therapy, the physical energy acts on the localized tissue area and induces mechanotransduction[12], stimulating the release of growth factors[13,14] and nitric oxide[15]. These effects, in turn, can enhance blood circulation and promote neoangiogenesis[16].

The goal of TPS is to provide an add-on therapy that is safe and could lead to improvement of symptoms. Stimulated areas can include the bilateral frontal cortex, bilateral lateral parietal cortex, extended precuneus cortex, and the bilateral temporal cortex. The usual treatment protocol consists of six sessions with 6,000 pulses over 2 weeks as the first treatment cycle.

The procedure is considered safe, as adverse events have been reported in about 4% of sessions characterized by moderate subjective severity that is transient and without a clear causal relationship to adverse device-related events (ADEs)[5].

While these initial results are encouraging, it is crucial for researchers and clinicians to assess whether TPS is appropriate for their specific applications. Factors to consider include the stage of Alzheimer's disease, patient response to other treatments, and the availability of facilities that can safely administer TPS under expert guidance. For individuals in the early to moderate stages of Alzheimer's, TPS may offer potential cognitive benefits with minimal side effects, but it is not yet considered a standalone treatment. Instead, it may complement existing therapies such as pharmacological interventions or cognitive training. Results of randomized-controlled trials are lacking to date. However, TPS might have the potential as an add-on treatment for Alzheimer's patients under controlled use and scientific exploration.

Protocol

The analysis of all TPS-treated patients was part of the local registry approved by the Ethics Committee of the Regional Medical Chamber (Ärztekammer Nordrhein, Nr. 2021026).

Moreover, all of the patients signed written consent to the treatment. A total of 11 patients were treated with TPS (nine men, two women, age range 59-77 years, M = 69.82). Before the treatment, all patients underwent a detailed informed consent process, during which they were thoroughly informed about the potential benefits and risks of transcranial pulse stimulation (TPS) with the NEUROLITH system.

1. Patient selection and preparation

1. Before starting this stimulation, patient selection and informed consent are crucial. Use the CE mark for Alzheimer´s Disease. Confirm diagnosis using CSF biomarkers on the basis of Alzheimer's clinical syndrome. Perform disease treatment according to national or international guidelines by a neurologist or psychiatrist.
   NOTE: TPS can be offered as an add-on under scientific exploration. Since TPS was administered as an add-on treatment, all patients continued with their regular medical treatment plans throughout the treatment. Some patients were on antidementia drugs and/or antipsychotics during the TPS sessions; however, these medications were not part of the study protocol and were not modified or standardized as part of the intervention.
2. Use the following exclusion criteria for TPS: Treatment is contraindicated with relevant intracerebral pathologies unrelated to Alzheimer's disease, including vascular encephalopathy, thrombosis in the treatment area, Fazekas grade 3, tumors, vascular malformations, metal implants, and cerebral amyloid angiopathy (CAA) as defined by the Boston criteria. Additional contraindications are a history of or ongoing antibody therapy, blood clotting disorders or oral anticoagulation, corticosteroid treatment within six weeks prior to the first application, epilepsy (either multiple seizures or a single seizure with a seizure focus), pacemakers not approved for TPS therapy, recurrent syncope, severe affective behavioral disturbances impacting daily life such as aggression or psychosis, pregnancy, and medical conditions that may lead to non-compliance with the protocol. With respect to diagnosis and exclusion criteria, including MRI, EEG, CSF analysis, lab tests, and detailed cognitive and affective assessments in the workup.

2. Neuropsychological testing

1. Perform neuropsychological testing before the first stimulation (baseline) and after the last stimulation (post-stimulation). The Alzheimer Disease Assessment Scale (ADAS) has been used for this study.
2. Before beginning the ADAS, prepare the testing environment to ensure it is quiet, comfortable, and free from distractions. Perform the assessment with a trained clinician or neuropsychologist, who follows a structured format to evaluate specific cognitive domains.
3. The ADAS consists of two main components: the Cognitive Subscale (ADAS-Cog) and the Non-Cognitive Subscale. Use the ADAS-Cog, which is most commonly used, to assess memory, language, orientation, and praxis through a series of tasks, as described below.
   1. Word recall: Present the patient with a list of words and ask to recall them immediately and after a delay.
   2. Naming objects and fingers: Show the patient a series of objects and ask to name them correctly.
   3. Following commands: Ask the patient to perform specific actions based on verbal instructions to assess comprehension and praxis.

4. Visuo-construction: Task the patient with copying geometric figures to evaluate visuospatial skills.
5. Ideational praxis: Ask the patient to demonstrate the use of common objects (e.g., a pencil or a comb).
6. Orientation: Question the patient about the current date, day of the week, and location.
7. Word recognition: Ask the patient to recognize previously presented words from a list of distractor words.
8. Language ability: Evaluate the patient's fluency and comprehension through structured conversations and sentence construction.

4. Use the non-cognitive subscale to assess behavioral symptoms such as mood changes, apathy, or agitation.
5. For consistency, ask the clinician administering the test to adhere strictly to the instructions outlined in the ADAS manual. Score each task based on performance, with higher scores indicating greater impairment.
6. After the last stimulation session, repeat the ADAS using a parallel version of the test to ensure that the results reflect genuine changes in cognitive function rather than practice effects.

3. Preparation of the device and environment

1. Turn on the device. Locate the main power switch at the back of the device and turn it on.
2. Press the standby button on the front panel. The device will take approximately 5 min to initialize.
3. Position the patient. Ensure the patient is comfortably seated, with possible neck support. Have the patient wear recognition glasses with detection lenses. Secure the glasses to the patient's head using tape or a strap to keep them in place.
4. Set up the camera. Align the camera to ensure the patient's head is fully visible within the frame. This camera is critical for tracking and calibration.

4. High voltage test (Daily maintenance)

1. Perform the High Voltage Test (HV-Test). Conduct this test once every 24 h. Follow the on-screen instructions to complete the test by pressing the trigger button on the handheld applicator.

5. Handpiece preparation

1. Prepare the handpiece by applying a drop of silicone oil onto the membrane of the handpiece.
2. Attach the prefilled coupling membrane (the distance piece) to the handpiece, ensuring it is secure for optimal performance.

6. Calibration for new patients

1. Load the patient's MRI data. For new patients, ensure the required MRI scans (T1-weighted, high-resolution images of the head from forehead to back, covering ear to ear) are available.
2. Insert the external storage device (USB or CD) containing the MRI data into the system's USB port.
3. Create a patient profile. Select **New Patient** in the system and enter the required information. When creating a new patient profile in the system, some information is automatically imported from the MRI-CD, while other details need to be entered manually.
    1. After inserting the CD into the system, the patient's full name and date of birth are automatically

retrieved from the metadata on the MRI CD. Manually input the treatment plan into the system. Select the preconfigured Alzheimer's Disease (AD) protocol, already stored in the system. This protocol includes the following settings: a frequency of 4 Hz, an energy level of 0.2 mJ/mm^2, and 6,000 pulses per session. The protocol can either be used as-is or adjusted based on the clinician's preferences.

4. Load the MRI data and verify the quality of the images. To verify the quality of the MRI data, manually scroll through the individual slices of the MRI images within the system. Ensure that all anatomical structures are sharp and well-defined and check for the absence of motion artifacts or distortions. Confirm that the overall resolution of the T1-weighted images is sufficient for accurate neuronavigation. Adjust image selections as necessary and proceed with calibration.

5. To calibrate the images, use the calibration pen to conduct a 3-point calibration using the following paths.
   Path 1: From the forehead to the back of the head.
   Path 2: From one ear to the other.
   Path 3: Perform circular or zigzag motions across the top of the head.

6. Ensure that the detection lenses are facing the camera at all times during calibration.

7. Confirm that the 3D head model on the screen aligns properly with the patient's head by rotating it to check contact points.

7. Treatment region setup (Optional)

1. Define treatment regions based on the patient's specific needs. For this study, the preconfigured Alzheimer's Disease protocol has been used including bilateral frontal lobe, bilateral parietal lobe, and precuneus. Additionally, to the initial protocol, add bilateral temporal cortex. Use the MRI images and specific anatomical landmarks of the brain to define the regions to be stimulated.

2. Adjust the size, shape, and number of treatment regions on the display. To adjust the ROIs, the process is performed entirely using the touch display controls.
   1. Begin by accessing the Treatment Planning module on the system's main interface. Within this module, select the **ROI Adjustment** option to enable editing of treatment regions. Once in the adjustment mode, the system displays a default ROI on the screen.
   2. To position the ROI over the desired anatomical area, such as the frontal lobe, parietal lobe, precuneus, or temporal cortex, use the arrow buttons on the touch display. The buttons allow to move the ROI incrementally in all directions (up, down, left, right) for precise alignment with the target brain region.
   3. After positioning the ROI, adjust its dimensions (size, depth, and shape) using the dedicated on-screen controls:
      Depth Adjustment (Button A): Tap the depth button and adjust the ROI's penetration level to match the treatment requirements.
      Width Adjustment (Button B): Use the width adjustment button to expand or contract the horizontal size of the ROI.
      Height Adjustment (Button C): Modify the vertical dimension of the ROI by tapping the height adjustment control. Save the settings once complete.

8. Conducting the treatment

1. Sequentially apply a generous amount of ultrasound gel onto the patient's scalp for optimal energy transmission.
2. Begin the treatment. Select the **Treatment Mode** on the device and confirm that the prefilled membrane is correctly attached. The correct attachment of the prefilled membrane is verified by ensuring it properly clicks into place on the handpiece. Optional the patient can use hearing protection during the session.
3. Hold the handpiece perpendicular to the patient's scalp, ensuring it is moved evenly across the surface. **Figure 2** illustrates the ideal alignment between the patient and the NEUROLITH during TPS. **Figure 3** shows an example of the regions of interest (ROI) and the modeling of tissue stimulated on a patient's MRI. **Figure 4** shows an illustration of the handheld device during stimulation.
4. Monitor the stimulation. Treat each region until the targeted areas on the display turn green, indicating proper coverage. Continue moving the handpiece while keeping the detection lenses in view of the camera to ensure continuous tracking.
   NOTE: If the recognition glasses shift slightly during treatment, the session can proceed. However, if the glasses are removed, recalibration is required.
5. Conclude the session. To end the treatment, press the **Stop** button on the device. The session end point is achieved when reaching 6000 pulses.

9. Post-treatment procedures

1. Clean the equipment. Clean the handpiece and the detachable membrane using approved wipes (avoid alcohol-based cleaners).
2. Patient care: Clean the scalp area gently to remove any remaining ultrasound gel. If necessary, dry the patient's hair with a towel or hairdryer. After the treatment, advise patients to remain nearby for the next 10-15 min in case they experience any delayed or mild side effects, such as dizziness, headache, or scalp discomfort, although no active observation is required. Encourage patients to stay hydrated, as this supports overall recovery and well-being. Advise patient to avoid intense physical activity for the rest of the day, particularly if they feel fatigued or experience any mild discomfort following the session.
3. Storage of treatment data: Save all treatment data, including defined regions, and adjust for future sessions. Any observations during treatment or feedback should be documented.

Representative Results

Transcranial pulse stimulation alleviated symptoms of Alzheimer's patients as demonstrated by uncontrolled pilot data from 11 patients (nine men, two women, age range 59-77 years, M = 69.82) published by the working group of this tutorial[1]. Stimulated areas included the bilateral frontal cortex, bilateral lateral parietal cortex, and extended precuneus cortex. The bilateral temporal cortex was added to the protocol. Treatment was administered in six initial sessions with 6,000 pulses over 2 weeks as the first treatment cycle.

The treatment protocol during stimulation involved 4 Hz, 0.20 mJ/mm^2, and 6000 pulses. Three out of 11 patients (27%) reported adverse events in three out of 75 total sessions (4%). These included jaw pain (NRS 4/10), nausea (NRS 7/10), and drowsiness (NRS 10/10). However, none of these lasted

more than 24 h, and not all could be directly attributed to the stimulation as adverse device events (ADEs).

A significant difference was observed in the post-stimulation ADAS total score compared to the baseline, with an improvement from 30.2 to 25.8 ($p = 0.01$), and in the ADAS-Cog score, which improved from 25.8 to 23.3 ($p = 0.04$; **Figure 5**). While some patients only showed minor improvements, the best improvement in a patient was 40%, leading to an overall improvement of 15.76% in the ADAS total score and 8.65% in the ADAS Cog score (**Figure 6**). Furthermore, a significant difference in depressive symptoms was detected in a self-reported subscale of the ADAS test. A one-tailed t-test showed a significant reduction in depressive symptoms, as measured by a self-reported subscale of the ADAS test. Before stimulation, the mean was 0.7 (SD = 1.1), and after stimulation, it decreased to 0.2 (SD = 0.4; $t(8) = 1.859$, $p < 0.01$).

A subjective rating scale was completed before and after the treatment period of two weeks. This scale allows patients to report their symptom severity and any perceived adverse events on a numeric rating scale of 0 to 10, with higher numbers indicating greater symptom intensity. The mean subjective improvement of the symptom severity, as measured by the NRS, was from 5.7 to 3.4 ($p = 0.023$).

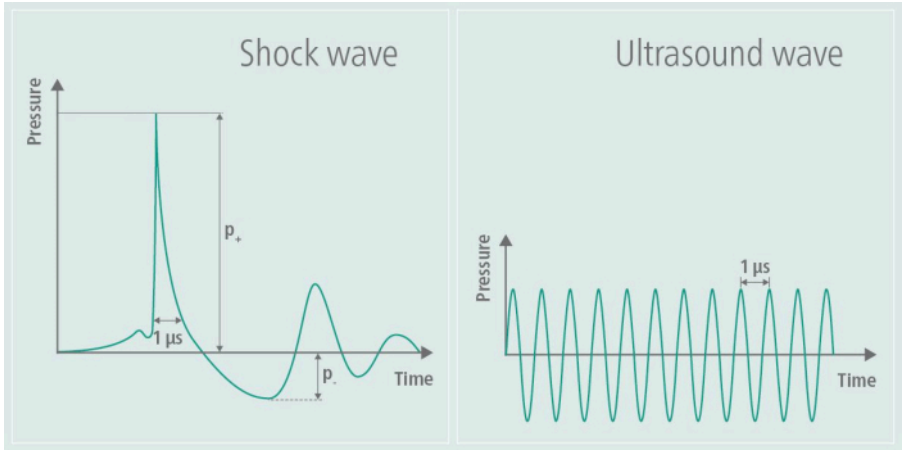

Figure 1: Shockwave during stimulation. The graph illustrates the amplitude of a TPS on the left side of the image and compares it with the amplitude of an ultrasound on the right side of the image. During TPS, a singular pressure pulse is generated, followed by a subsequent flattening of the amplitude. In contrast, the amplitude of ultrasound does not flatten out again but is maintained, resulting in continuous high-frequency oscillations over time. This figure has been modified from[9].

Please click here to view a larger version of this figure.

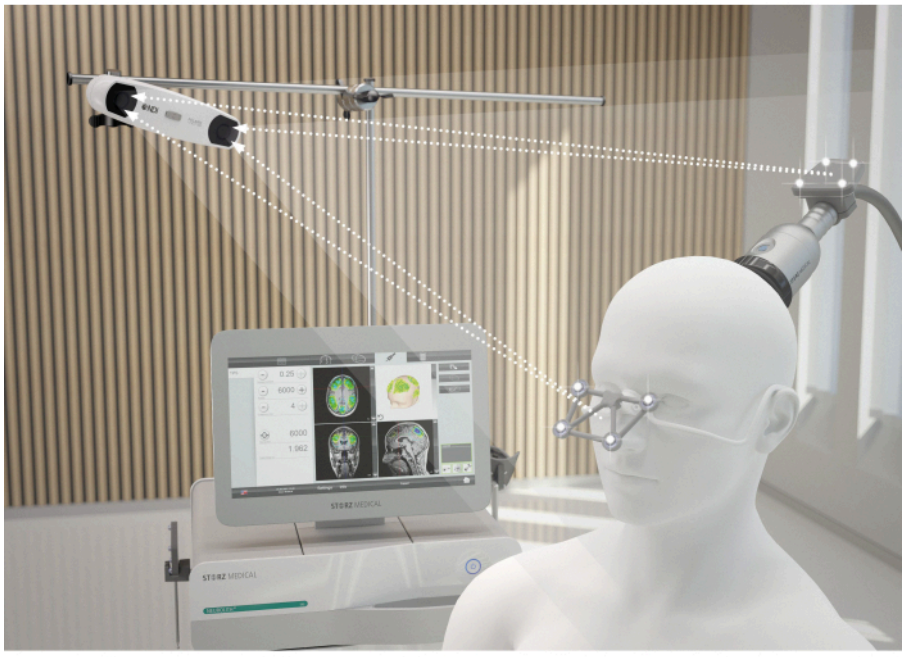

Figure 2: MRI navigation system. The image illustrates the ideal alignment between the patient and the NEUROLITH during TPS. The 3D camera contacts the detection lenses of the goggle and those of the handpiece. Only if this transmission is guaranteed is the handpiece recognized in the correct spatial position and the visualization of the stimulation on the screen is undisturbed. This figure has been modified from[9]. Please click here to view a larger version of this figure.

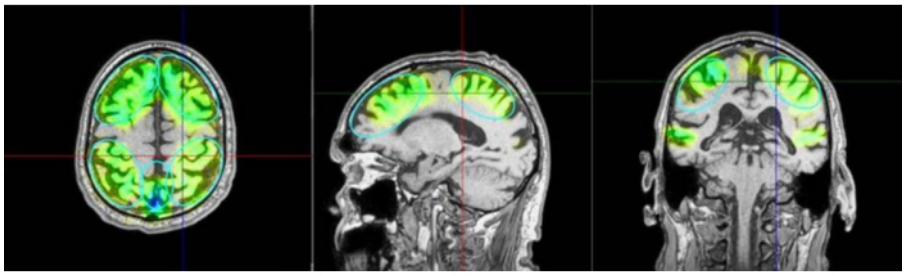

Figure 3: Regions of interest and stimulated areas. The image shows an example of the regions of interest (ROI) and the modeling of tissue stimulated on a patient's MRI. The colors further differentiate the number of pulses applied in the respective areas of the precuneus, as well as frontal and parietal regions. The green coloring is followed by turquoise, blue, and violet. Violet indicates excessive intensity and must be avoided. Stimulated areas are visualized as simulated data from the navigation system as mainly reached areas, but this is not measured as real applied brain activation. Additional temporal stimulation is added in the Kempen protocol although it is not predefined as ROI. left: axial view, middle: sagittal view, right: coronal view. Please click here to view a larger version of this figure.

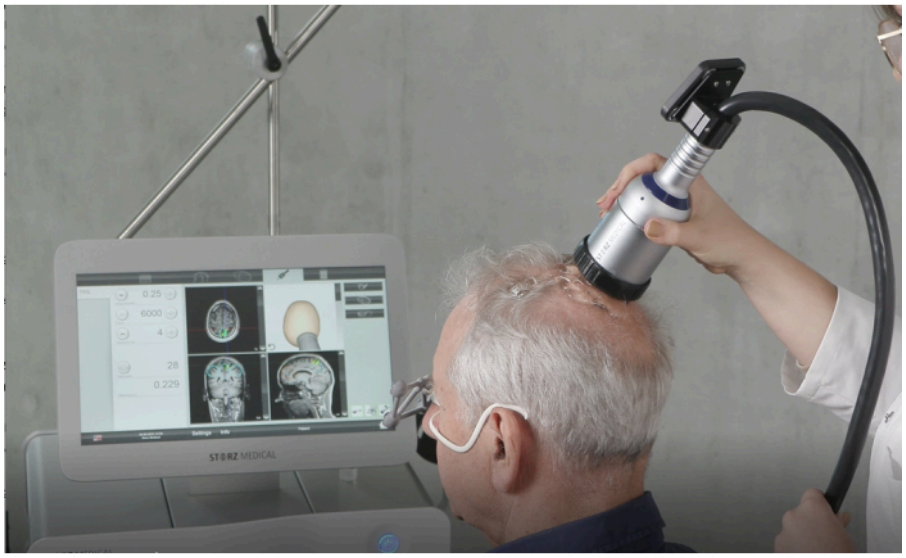

Figure 4: Handheld device. This figure illustrates the handheld device in use during stimulation. Critical preparatory steps include applying a sufficient amount of ultrasound gel to the patient's scalp to ensure optimal energy transmission and verifying that the pre-filled membrane is securely and correctly attached. During treatment, the handpiece is held perpendicular to the scalp and moved evenly across the surface to maintain consistent stimulation. This figure has been modified from[9]. Please click here to view a larger version of this figure.

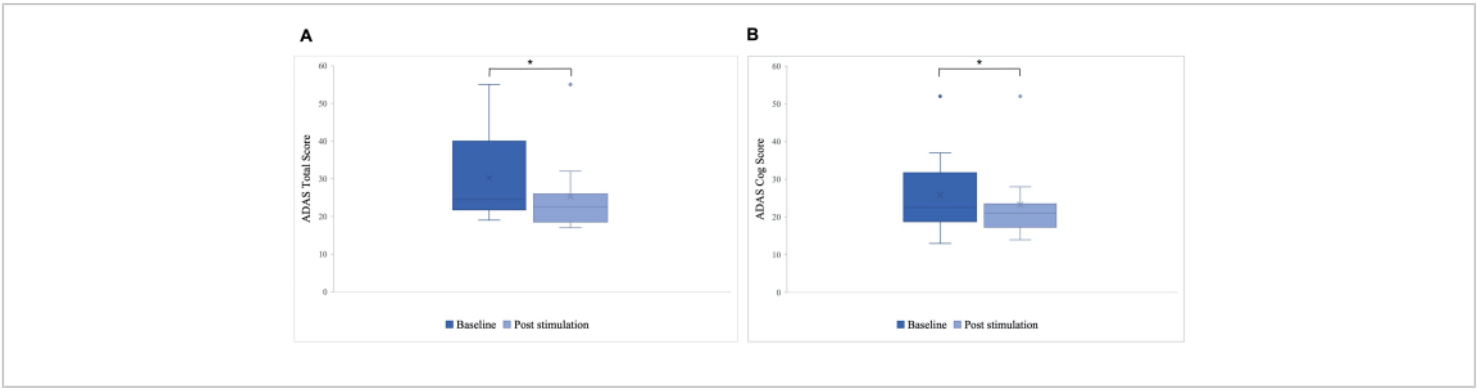

Figure 5: Alzheimer's Disease Assessment Scale (ADAS) before the first stimulation. Mean of the patient group's score on the Alzheimer's Disease Assessment Scale (ADAS) before the first stimulation (dark blue) and after the last stimulation (light blue). A lower score indicates better performance. The box plot shows the distribution of the patients' data. (**A**) ADAS total score. The line represents the median of the group (baseline = 24.5, post-stimulation = 22.5), and the cross represents the mean scores (M baseline = 30.2 (SD 11.55), M post-stimulation = 25.8 (SD 10.71), *p = 0.01). (**B**) ADAS cog score. The line represents the median of the group (baseline =22.5, post-stimulation = 21), and the cross represents the mean scores (M baseline = 25.8 (SD 10.77), M post-stimulation = 23.3 (SD 10.27), *p = 0.04). This figure has been modified from[5]. Please click here to view a larger version of this figure.

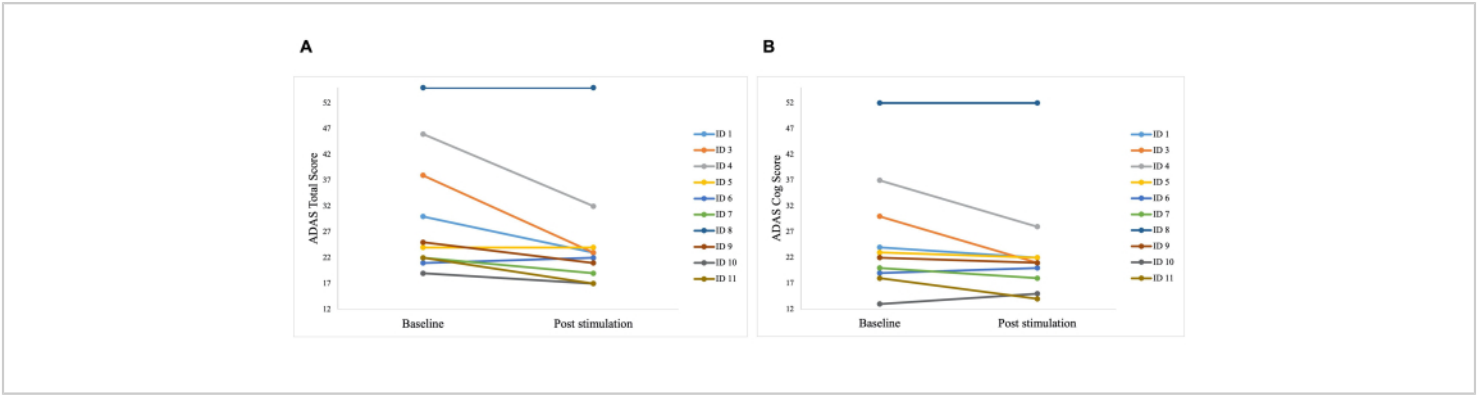

Figure 6: Individual test results of the patients in ADAS. Individual test results of the patients in Alzheimer's Disease Assessment Scale (ADAS) before the first stimulation (baseline) and after the last stimulation (post-stimulation). A lower score indicates better performance. Each line represents one patient. (**A**) Individual scores of each patient in the ADAS total score. The best improvement was 15 points (ID 3). (**B**) Individual scores of each patient in the sub scale ADAS cog score. The best improvement was 14 points (ID 3 and ID 4). This figure has been modified from[5]. Please click here to view a larger version of this figure.

Discussion

Overall, TPS is a possible treatment for Alzheimer's disease. From a practical standpoint, the stimulation process is designed to be user-friendly for the operator. The ability to define regions of interest at the start of the procedure, along with the visualization of the number of pulses applied through color-coded markings during treatment, significantly simplifies the handling of the user interface. The setting of the regions of interest can also be freely selected and adjusted as needed. Stimulated areas are clearly visualized as simulated data, though further development by the manufacturer is necessary to display deeper areas affected by the device at lower energy levels.

Critical steps in the TPS protocol include the precise placement of the stimulation device over the targeted brain regions, ensuring the correct intensity and frequency of pulse waves, and careful monitoring of patient responses. Troubleshooting might include ensuring optimal contact between the handpiece and the scalp to prevent energy loss or suboptimal stimulation. If discomfort or side effects are observed, intensity adjustments or repositioning may be required.

Published uncontrolled data have demonstrated clinical cognitive improvements[5,3], as well as increased cortical thickness in several brain areas[10] and changes in MR-network connectivity[11]. Improvements in mood have also been reported[5,4]. Compared to other non-invasive brain stimulation methods, TPS offers several distinct advantages. First, it combines mechanical shockwaves with precise neuronavigation, allowing targeted application to affected brain regions. Unlike TMS, which typically only stimulates superficial cortical layers, TPS's depth of penetration makes it particularly suited for treating neurodegenerative diseases like Alzheimer's, where deeper brain structures are involved. Additionally, TPS appears to have a favorable safety profile, with minimal and transient side effects reported in only 4% of treatment sessions, indicating that it may be a more tolerable option for patients with moderate-to-severe AD[5].

To thoroughly investigate the mechanisms of action and conduct a detailed analysis of potential risk factors associated with TPS therapy, additional foundational studies are required.

In a recent study published by this research group, brain network activity in Alzheimer's patients was examined before and after transcranial pulse stimulation (TPS)[17]. The results indicate that TPS can modulate brain oscillations and connectivity, potentially improving cognitive function in Alzheimer's disease. One of the proposed mechanisms is that the increased gamma oscillations post-TPS may facilitate glymphatic clearance in the brain. This possible effect on glymphatic clearance should be further investigated in future studies. Additionally, further mechanistic studies are needed to clarify how TPS influences brain network physiology and whether its neuroprotective effects can slow or halt the progression of Alzheimer's.

Preclinical animal studies that explore the effects of TPS on both healthy and diseased brains are crucial to gaining a deeper understanding of the underlying mechanisms. It is important to note that various NiBS techniques operate through distinct mechanisms[1]. Therefore, it is essential to investigate whether and how the effects described for ultrasound therapy[18] and shockwave therapy[6] on tissue play a role in TPS therapy. The former described the possible influence of TPS on mechanotransduction processes, as well as its potential to induce vascular, cellular, and molecular changes, which

must be thoroughly investigated. Furthermore, the modulation of neuroinflammatory processes, with particular emphasis on blood-brain barrier dynamics, presents an intriguing area for future research. Understanding these effects could provide valuable insights into the underlying mechanisms and help optimize TPS for therapeutic applications. Further, this contributes to exploring the potential application of TPS treatment in the management of other neurodegenerative diseases.

TPS shows promise as a therapeutic approach; however, several limitations must be addressed. Controlled clinical trials with placebo groups are essential to accurately delineate the specific effects of TPS. A significant challenge is the high inter-individual variability in response to stimulation, which may be influenced by factors such as the stage of Alzheimer's disease (AD) and the presence of comorbidities[4]. Additionally, the optimal protocol for long-term treatment remains undefined. Current approaches include monthly single booster sessions or repeating a treatment cycle of 12 sessions within a year, but evidence supporting the superiority of one approach over the other is lacking. Future clinical research should prioritize identifying optimal stimulation parameters, evaluating how patient-specific factors (e.g., stage of AD) influence therapeutic outcomes, and investigating the long-term effects and sustainability of TPS therapy.

Disclosures

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