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Neuromodulatory Effects of Neuronavigated Transcranial Pulse Stimulation (TPS): A Systematic Review

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Abstract

Transcranial Pulse Stimulation (TPS) has emerged as a non-invasive, ultrasound-based neuromodulation technique showing promise in treating various neurological conditions, especially Alzheimer's disease. However, its effectiveness for other neurodegenerative, developmental, and psychiatric conditions is still under active investigation. This systematic review aims to evaluate the current evidence on the effectiveness of TPS across a variety of conditions, including both clinical and healthy populations. PubMed, Cochrane Library, Google Scholar, Scopus, and Web of Science were searched, and 15 studies were included regardless of their study design. The qualitative evaluation of the findings suggested that neuronavigated TPS evoked significant improvements in cognitive and motor functions, and the global efficiency of functional connectivity without causing serious adverse effects. However, a caveat should be noted, as more experimental control is needed in this field. To better present TPS's potential therapeutic effects, future studies should also prioritize stimulating deeper brain regions, using more precise stimulation targets, as well as employing larger sample sizes.

Keywords: Transcranial Pulse Stimulation, Transcranial Shockwaves, Neuromodulation, Mechanotransduction, Ultrasound, Cognitive Functions, Neurodegeneration, Neurocognitive Disorders, Alzheimer's disease, Depression,

Neuromodulatory Effects of Neuronavigated Transcranial Pulse Stimulation (TPS): A Systematic Review

1. Introduction

The emergence of electroconvulsive therapy in the 1930s marked a significant milestone in the history of neuromodulation (Hoy & Fitzgerald, 2010). This significant development not only revolutionized psychiatric treatment but also raised a strong desire to search for alternative methods that could modulate brain activity without the need for invasive surgeries. Since then, this pursuit has yielded a diverse array of non-invasive brain stimulation (NIBS) modalities, each with its unique mechanisms and applications. Over the past decades, NIBS techniques have become essential tools for studying and modulating brain functions and have been utilized for both therapeutic and research purposes (e.g., Hallett, 2000; Nitsche, 2008). Developments in neurotechnology have allowed physicians and researchers to apply non-pharmacological treatment options to people diagnosed with various neurological and psychiatric conditions. The ability to induce facilitation and/or inhibition without the need for invasive brain surgery makes NIBS a particularly practical method. Additionally, this ability also allows researchers to infer causal relevance of functions of targeted brain regions in a given task (Hartwigsen & Silvanto, 2023).

Among the most prominent and widely adopted NIBS methods are Transcranial Magnetic Stimulation (TMS) and Transcranial Electrical Stimulation (tES). To begin with, TMS utilizes magnetic fields to induce electrical currents in targeted brain regions, offering a noninvasive means of modulating neural circuits implicated in various neurological and psychiatric disorders (e.g., Chervyakov et al., 2015). It has found widespread applications. For instance, some protocols of repetitive TMS (rTMS; that is, recurring TMS pulses over a short period of time) have

demonstrated efficacy in alleviating symptoms in the treatment of depression (Perera et al, 2016), improving mood regulation (George et al., 1995), improving trained associative memory (Bagattini et al., 2020) and cognitive functions in patients with Alzheimer's disease (AD) (Leocani et al., 2021), and ameliorating motor and nonmotor symptoms in Parkinson's disease (PD) (Zhuang, 2020). Additionally, TMS also alters brain connectivity patterns. For example, normalized abnormal brain connectivity patterns in PD patients were found after stimulation of the supplementary motor area with high-frequency rTMS (10 Hz) (Mi et al., 2020). Regarding the treatment of depression, Eshel and colleagues (2020) revealed that rTMS (high frequency, 10 Hz) on left dlPFC resulted in increased dlPFC global connectivity and decreased amygdala – dlPFC connectivity. In addition to patient groups, Jung and coworkers (2020) showed that the stimulation of M1 of 36 right-handed healthy adults with 1 Hz TMS reduced activation of the right motor network during the task and increased network deactivation of the left motor network at rest condition, and as well as induction of interhemispheric inhibition during motor execution. Additionally, the authors stated that the Rolandic Operculum Network and Insular Network showed increased network activation which might be resulted from multisensory experience from M1 TMS. In comparison to TMS, tES involves applying a low-intensity electrical current to the scalp to influence brain activity (Reed & Cohen Kadosh, 2018). The primary mechanism of tES involves the modulation of neuronal membrane potentials (Vöröslakos et al., 2018). By delivering a constant (in transcranial direct current stimulation, tDCS) or alternating (in transcranial alternating current stimulation, tACS) current through electrodes placed on the scalp, tES can either depolarize or hyperpolarize neuronal membranes, thereby altering their excitability. Depolarization tends to make neurons more likely to fire action potentials, enhancing cortical excitability, while hyperpolarization makes neurons less likely to fire, reducing cortical excitability

(Fertonani & Miniussi, 2017). These changes in excitability can modulate brain function and are thought to underlie the therapeutic effects of tES in conditions such as depression, anxiety, and cognitive impairment. For instance, it was found that tDCS significantly improves depressive symptoms of the active group compared to the sham-control group (Pavlova et al., 2018; Zhang et al., 2021; Zhou et al., 2020). Additionally, tDCS was shown to be effective in mood symptom relief (Rao et al., 2018) and subjective emotional experience (Abend et al., 2019), improvements in associative memory especially when the parietal cortex was stimulated (Bjekić et al, 2023), and in episodic memory (Sandrini et al., 2020). Moreover, as in TMS, tES also alters brain connectivity. Tecchio and colleagues (2018) supported this by revealing that cathodal tDCS modulated functional connectivity in focal epilepsy patients which led to reduced epileptic seizures. Mondino and colleagues (2020) also showed similar results with healthy participants by finding increased resting-state functional connectivity (rsFC) between left dlPFC and bilateral parietal regions after tDCS and between left dlPFC and right parietal lobule after tACS.

Although TMS and tES have garnered significant attention, both techniques have some limitations, especially in their inability to stimulate deep brain regions. These limitations have led researchers to seek new NIBS methods. This quest has led to the investigation of acoustic/ultrasound-based stimulation methods in recent years.

1.1. Overview and Brief History of Transcranial Pulse Stimulation (TPS)

The use of ultrasound for neuromodulation dates back to the 1950s. In 1958, Fry and colleagues published the first neuromodulation study utilizing ultrasound on animals. In this study, authors achieved inhibition of visual evoked potentials in the cat brain, which was fully reversible.

Since then, in comparison to electrical and magnetic techniques, the potential of using ultrasound has been mostly left unnoticed until the recent uprise. Following Clement & Hynynen's remarkable achievement of developing a hemisphere-shaped transducer for delivering focused ultrasound with CT-based registrations in 2002, it has been shown that acoustic waves can be focused on brain tissue with millimetric precision for noninvasive brain surgery and therapy. According to the literature, the first human neuromodulation study using transcranial unfocused ultrasound (TUS) was conducted by Hameroff and colleagues (2013). In this double-blind, sham-controlled pilot study, researchers recruited patients with chronic pain, and TUS was targeted at the posterior frontal cortex. Subjective reports revealed that perceived pain was slightly improved, and participants' mood/global affect was significantly enhanced 10- and 40-minutes posterior to stimulation. Regarding the first transcranial focused ultrasound stimulation (tFUS), Legon and his colleagues (2014) showed that modulating the primary somatosensory cortex (S1) of healthy participants with tFUS can significantly reduce the amplitude of somatosensory evoked potential (SEP), and boost performance on sensory discrimination task.

Like other techniques, transcranial ultrasound stimulation also has different variations depending on its waveform that operates within the same ultrasound frequency range (Truong et al., 2022). Transcranial low-intensity/focused ultrasound stimulation (LITUS/tFUS) utilizes continuous acoustic waves which can either excite or inhibit neural activity (Fomenko et al., 2018). Darmani and colleagues (2022) proposed three dominant working mechanisms of LITUS/tFUS: cavitation, thermal change, and mechanical deformation. To sum up the proposed mechanisms, cavitation term suggests that ultrasound waves can cause the formation of bubbles in the neuronal membrane leading to capacitance changes. Thermal change refers to the ability of biological

tissues to absorb ultrasound waves and convert it into heat, and in this way, neuronal activity is modulated by the response to local temperature changes. Lastly, mechanical deformation stands for the added pressure by ultrasound waves on variety of ion channels which leads to modulated occurrence of action potential. During the past decade, the LITUS/tFUS technique has been shown to safely modulate brain activity in human cortical and subcortical regions. To illustrate, Lee and colleagues (2015) examined the effects of image-guided tFUS on the somatosensory cortex of healthy volunteers. The authors stated, "The sonication elicited transient tactile sensations on the hand area contralateral to the sonicated hemisphere, with anatomical specificity of up to a finger, while EEG recordings revealed the elicitation of sonication-specific evoked potentials." (p. 1). In addition to this, Legon and colleagues (2018) revealed that stimulation of the unilateral sensory thalamus resulted in inhibition of the P14 SEP in the verum compared to sham stimulation. Moreover, behavioral assessments showed that participants' performance on a sensory discrimination task worsened significantly in the active stimulation group. In another study targeting subcortical regions, tFUS was employed to stimulate the bilateral hippocampus of AD patients and the substantia nigra of PD patients (Nicodemus et al., 2019). The authors claimed that 62.5% of all participants showed significant improvements on at least one cognitive measure, and motor scores of 87% of all participants were either stable or improved. In terms of modulating functional connectivity, Yaakub and colleagues (2023) revealed that LITUS targeting the dorsal anterior cingulate cortex (dACC) and the posterior cingulate cortex (PCC) of healthy participants resulted in increased rsFC in both regions compared to sham condition.

In comparison with LITUS/tFUS, Transcranial Pulse Stimulation (TPS) utilizes a single ultrashort high-intensity ultrasound pulses (~3 μs) repeated every 200 to 300 ms (Truong et al.,

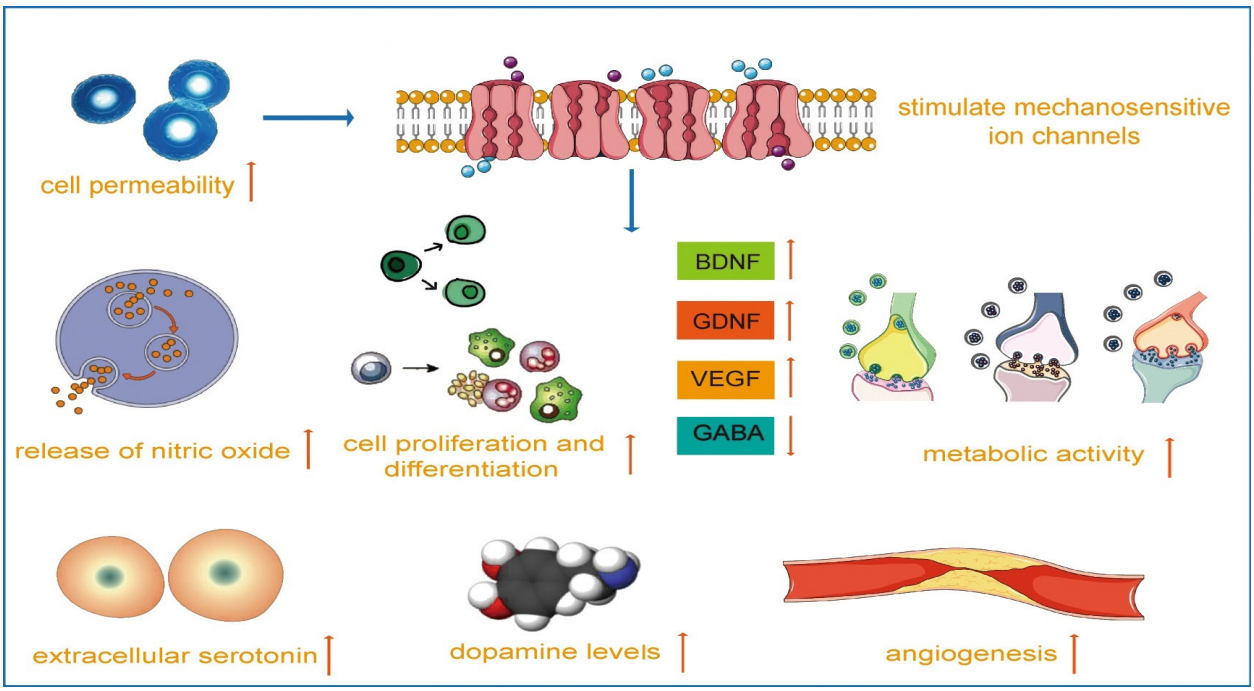
2022). In addition, mechanical ultrashort pulses of TPS are also called shock waves. (Cont et al., 2022). In this regard, the first clinical trial by Lohse-Busch, Reime & Falland was published in 2014. In that study, non-navigated form of ultrasound pulse technology, as an add-on therapy, was used for transcranial neuromodulation in five patients with unresponsive wakefulness syndrome over at least 5 years. Their results showed a series of improvements: 135.90% on the German Coma Remission Scale (KRS), 43.6% on the Glasgow Coma Scale (GCS), four patients initiated non-verbal communication, and removal of PEG feeding tube in three patients. Their longitudinal study has left a remarkable impact considering the patients with severe brain damage had not been responsive to any other type of treatment for many years. This significant study was followed by a case report utilizing MR-navigated ultrasound pulse technology. Monti and colleagues (2016) targeted the right thalamus of a patient with a score of 3 on the GCS and loss of consciousness more than 24 hours after traumatic brain injury. After stimulation, the patient showed improvements in reaching towards objects and reliable communication, full language comprehension three days after the treatment, and attempted walking after 5 days. Regarding the current state of neuronavigated TPS which received European Union (CE) approval for treatment of neurological disorders in 2018, the first clinical study was published in 2019 by Beisteiner and colleagues. The details of the study will be given in the further sections of this review.

Exposure of biological cells to physical forces is not a new concept. All biological cells dynamically comply their behaviors with their environmental forces. These forces can be resulted from neighbor cells and the surrounding extracellular matrix (Rocha et al., 2022). This adaptive strategy is called mechanotransduction, and it is defined as biological responses arising from

mechanical force conversion in various cell types such as epithelial, neuronal, and muscle (Ingber, 2006; Martino et al., 2018; Wang, 2017).

Figure 1

Biological Mechanism of Mechanotransduction by TPS



Note: Adapted from Chen et al., 2024.

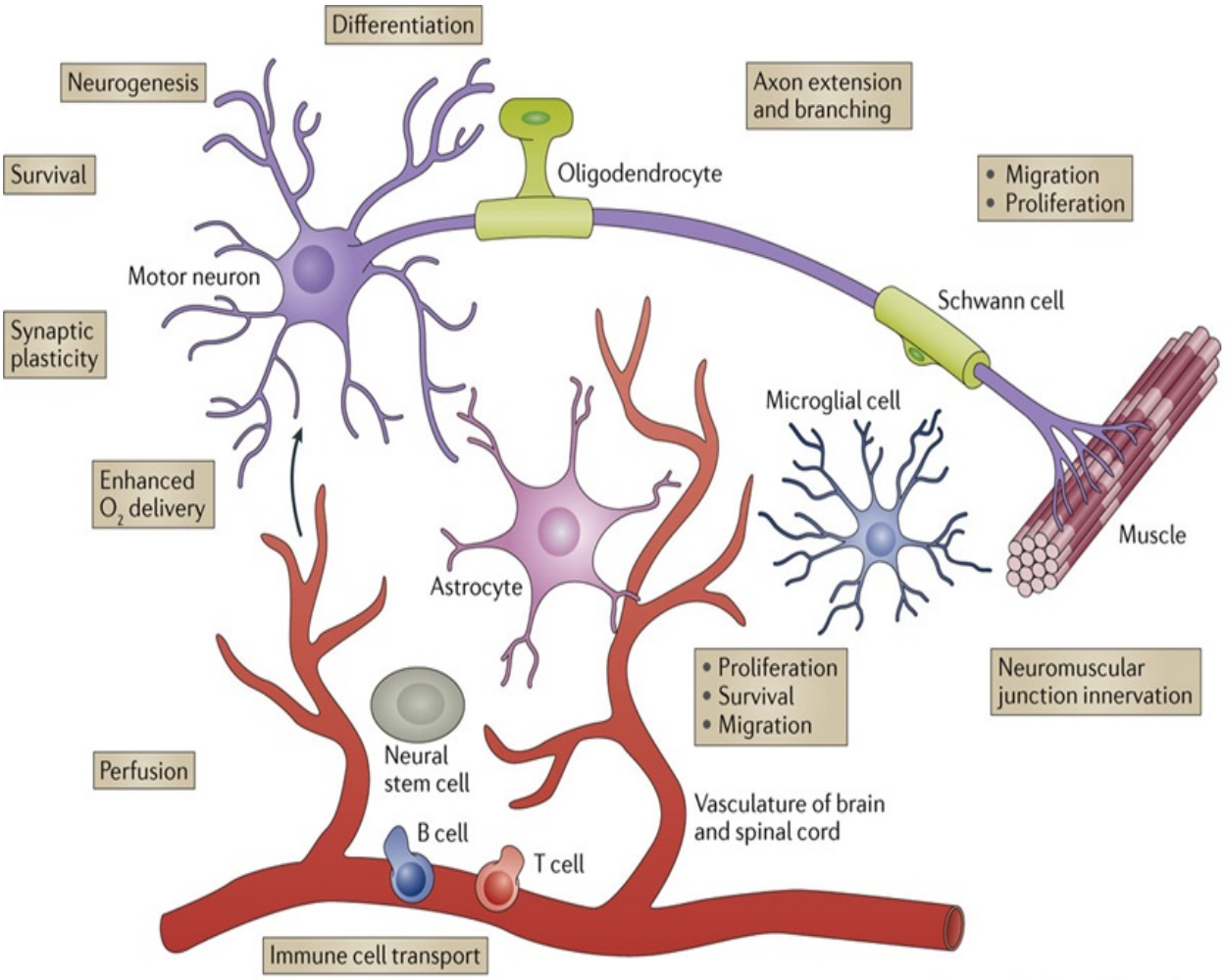
Mechanotransduction through the stimulation of mechanosensitive ion channels as a result of increased cell permeability is the basic mechanism of TPS (Cheung et al., 2024). During intervention, neurons convert received TPS pulses into biological responses such as cell migration, proliferation, differentiation, increase in extracellular serotonin and dopamine levels, and apoptosis which result in various biological effects (*Figure 1*). To begin with, TPS initiates growth factor expressions such as brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), (Beisteiner et al., 2020), and vascular endothelial growth factors (VEGF) (Yahata et al., 2016). BDNF is one of the neurotrophic factors that has a variety of

beneficial functions in the development, survival, and maintenance of neuron cells in the central nervous system (CNS), and it plays an important role in neurogenesis. Evidence has shown that BDNF makes substantial contributions to neurogenesis and synaptic plasticity through various signaling pathways, and its dysfunction leads to neurodegenerative and psychiatric disorders (Numakawa, Odaka, & Adachi, 2018). In a similar fashion, VEGF plays multiple important roles in CNS (*Figure 2*), and reduction in its levels is related to neurodegenerative diseases. In addition to neurogenesis, VEGF is also involved in the formation of new blood vessels (angiogenesis), transportation of immune cells, and maintenance and survival of endothelial cells in cerebral blood vessels (Lange et al., 2016).

Besides affecting growth factor expressions, TPS also impacts the release of nitric oxide (NO), which in turn influences multiple processes like vasodilation, increased metabolic activity, and angiogenesis. Picón-Pagès and colleagues (2019) supported this by stating that “Nitric oxide (NO) works as a retrograde neurotransmitter in synapses, allows the brain blood flow and also has important roles in intracellular signaling in neurons from the regulation of the neuronal metabolic status to the dendritic spine growth”. More importantly, NO has a particular anti-inflammatory effect, as it is highly expressed in microglia and astrocytes, which are responsible for cleaning metabolic waste such as excess neurotransmitters, stabilizing and regulating the blood-brain barrier (BBB), promoting synapse formation, and responding to pathogens and injury (Yuste et al., 2015).

Figure 2

Vascular Endothelial Growth Factors (VEGF) in CNS



Note: Adapted from Lange et al., 2016. Copyright 2016 Springer Nature. Reprinted with permission.

When all these biological effects are taken into account, TPS seems to be a particularly good technique for the treatment of neurodegenerative diseases, especially those which require interventions on the deep brain regions.

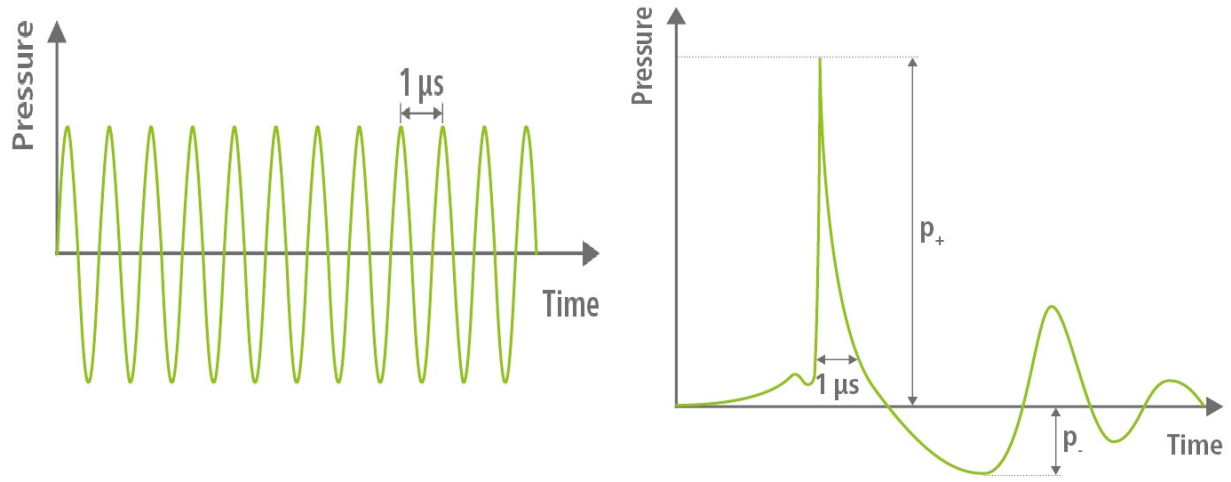
1.2. Comparison with Other Neuromodulation Techniques

To date, the most widely investigated and used NIBS technologies are TMS and tES. The fact that they are portable and easy to apply has increased the feasibility of these techniques. However, these NIBS methods have had serious limitations. First of all, the inability to reach deep brain areas is the biggest limitation of electrical and magnetic techniques. As an example, TMS can usually reach the brain areas that are 2 to 4 cm below the surface (Deng et al., 2013; Gomez et al., 2018; Lefaucheur et al., 2014). This limitation prevents them from being used for therapeutic purposes that require intervention in deep brain areas, such as in thalamic disorders. TPS, on the other hand, can successfully target deep brain areas up to 8 cm which allows reaching, for example, the thalamus, which lies between 5 and 6.5 cm below the scalp (Cheung et al., 2024; Matt et al., 2022). In support of this, before conducting the first clinical trial, Beisteiner and colleagues (2020) performed human skull and brain sample measurements to identify the transversal (beam width) and axial (beam length/range) resolutions of TPS, as well as skull attenuation. The authors remarked approximately a few millimeters of the transversal resolution, and the axial resolution around 60-80 millimeters. In addition to their inability to reach deeper regions, conventional NIBS methods also suffer from poor spatial resolution compared to acoustic techniques due to rapid attenuation of the electrical field. For instance, Deng and colleagues (2013) stated that figure-8 and circular TMS coils have a focality of 5 cm^2 to 34 cm^2, respectively, which however also depends on pulse intensity. In comparison, according to Lee and colleagues (2016), fTUS provides a spatial resolution of 2 to 10 mm. Similarly, TPS also shows transversal resolution of a few millimeters, which refers to the spot size diameter or width of the TPS beam (Matt et al., 2022). Another limitation of TMS and tES is that both techniques suffer from electrical conductivity meaning the ability of electrically active cells to generate and transmit electrical impulses in the

surrounding tissues, which also affects spatial resolution. Since TMS and tES create electrical fields to stimulate the targeted brain area, the field distribution is highly affected by different conductivity properties of tissue and Cerebro Spinal Fluid (CSF) (Minjoli et al., 2017). This limitation also leads to secondary stimulation maxima issues. Siebner and colleagues (2022, p. 60) explained this by stating that "Neuronal excitation spreads ortho- and antidromically along the stimulated axons and causes secondary excitation of connected neuronal populations within local intracortical microcircuits in the target area". Therefore, the excitation or inhibition can spread regionally, and as a result, might affect the neuroimaging results and stimulation outcomes. Conversely, fTUS/LITUS or TPS minimizes this limitation as both techniques are dependent on acoustic properties (Legon et al., 2018). This feature of ultrasonic methods also eliminates the problem of simultaneous acquisition of electrophysiological signals which leads to the prevention of electrical artifacts during EEG recordings (Lambert, 2023). When comparison of the acoustic (ultrasonic) techniques is concerned, fTUS/LITUS can cause tissue heating due to its continuous wave characteristics and standing wave phenomena (Mueller et al., 2017). Standing wave phenomena are due to the occurrence of reflected ultrasound waves from a surface in the direction of the transducer (Collins et al., 2021). Reflected and emitted waves can cumulate, and result in pressure and heat changes. In comparison, TPS overcomes standing wave phenomena and heating because it is characterized by a single ultrashort pulse with a high amplitude followed by a counter-tension wave with a lower amplitude (Sprick & Köhne, 2022) (*Figure 3*). In conclusion, considering all the aforementioned advantages, TPS can outperform the existing NIBS methods and yield superior results.

Figure 3

The Difference between Ultrasound wave Profiles of fTUS/LITUS (left) and TPS (right)



Note: Adapted from Sprick & Köhne, 2022. Copyright 2022 IEEE. Reprinted with permission.

1.3. Rationale and Objectives of This Review

Even though TPS is one of the latest NIBS techniques, it offers several conspicuous advantages such as mitigated conductivity and tissue heating, high spatial resolution, and the ability to reach deep brain areas. However, to our knowledge, there is no systematic review to collect all TPS studies to combine the results, summarize, address the limitations, and suggest future directions. Thus, the objectives of this review are as follows: to assess the effectiveness of TPS in modulating neural activity across different neurological and psychiatric conditions as well as in healthy populations, to evaluate the safety profile of TPS and its adverse effects, to identify the limitations of the existing literature including methodological considerations, sample sizes, and outcome measures, and finally, to suggest future directions to facilitate the development of more effective targeted interventions.

2. Methods

For this review, the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) criteria were followed (Page et al., 2021). This review was preregistered into Open Science Framework (OSF) (osf.io/hq7um).

2.1. Search Strategy

Included studies were searched through PubMed, Cochrane Library, Google Scholar, Scopus, and Web of Science from inception to date. Only articles in English were considered. The following keywords were used: ("Transcranial Pulse Stimulation", OR, "TPS", OR "Pulsed Ultrasound Stimulation"). Subsequently, to exclude studies with other intervention techniques, the search criteria were extended as (NOT "Transcranial Magnetic Stimulation", NOT "Transcranial Electrical Stimulation", NOT "TMS", and NOT "tDCS"). In addition, reference lists of review articles were also inspected for additional relevant articles. Further details of the search strategy were demonstrated in Appendix 1.

2.1.1. Inclusion and Exclusion Criteria

The inclusion/exclusion criteria were applied in accordance with PRISMA guidelines. The titles and abstracts were assessed prior to the identification of inclusion/exclusion criteria. After the title and abstract assessment, the inclusion criteria were identified as follows: (i) Utilization of neuronavigated TPS intervention, (ii) Uncontrolled and controlled trials of TPS with human subjects regardless of participants' neurological and psychiatric conditions, and (iii) details of outcome measures were provided. The exclusion criteria were defined as follows: (i) animal or

computational studies, (ii) conference posters, (iii) case reports, (iv) scientific letters, (v) study protocols, and (vi) different interventions related to fTUS/LITUS or other NIBS techniques. Studies were automatically excluded if the title was not relevant to TPS. If the title or abstract were unclear, the entire article was assessed.

2.1.2. Screening Process

Identified articles were exported to the Rayyan online tool in accordance with its file compatibility for screening (Ouzzani et al., 2016). First of all, the duplicate detection tool was used to detect duplicates. After the process, suggestions of the AI tool were inspected to review the data for duplicate removal. During data revision, the exported articles were labeled according to the type of study to facilitate inclusion and exclusion before screening. Then, screening of abstracts was performed for additional labeling such as including different interventions and medication. As a final check, full-text versions of articles were uploaded for full-text screening in accordance with inclusion/exclusion criteria.

2.2. Data Extraction

For all included studies, data extraction consisted of identifying study characteristics (authors, publication year, study design, and sample size), participant demographics (age, sex, disease type, and severity), stimulation protocols (duration and site, pulse repetition frequency, energy flux density, number of pulses), and outcome measures that quantify mood, cognitive and motor functioning as well as neuroimaging results (See Table 1 for outcome measures). Quantitative data for pre- and post-intervention from both the stimulation and control (sham) conditions were extracted from the results text, tables, and figures.

2.2.1. Variables of Interest

Like other NIBS techniques, TPS might also induce alterations in mood, cognitive, and motor functioning by modifying brain activity, as well as structural and functional connectivity. The outcome measures used in the included studies were chosen based on the specific characteristics and needs of various clinical and non-clinical populations, including individuals diagnosed with AD, PD, Mild Neurocognitive Disorder (NCD), Major Depressive Disorder (MDD), autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), as well as healthy participants.

For populations with AD and NCD, the studies primarily utilized cognitive and functional assessment tools to evaluate the impact of TPS. These included the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), the Alzheimer's Disease Assessment Scale (ADAS), the Mini-Mental State Examination (MMSE), the Stroop test, and the Montreal Cognitive Assessment (MoCA), which assess various aspects of cognitive functioning such as memory, attention, and executive function. To evaluate functional independence and daily living activities, the Pfeffer Functional Activities Questionnaire (P-FAQ) and the Lawton Instrumental Activities of Daily Living Scale (IADL) were employed. Additionally, behavioral and psychological symptoms in these populations were assessed using the Neuropsychiatric Inventory (NPI). Advanced neuroimaging techniques like fMRI, and EEG were utilized to monitor structural and functional changes in the brain in response to TPS.

In one of the included studies that involve PD patients, researchers focused on both cognitive and motor outcomes. Motor function was measured using the Unified Parkinson's

Disease Rating Scale (UPDRS-III), which evaluates motor symptoms including tremor, rigidity and bradykinesia, and fine motor skills.

For individuals diagnosed with MDD in one of the included studies and comorbid depressive symptoms in patients with AD and NCD, the studies included several standardized mood and affective symptom assessments to determine the effects of TPS. The Beck Depression Inventory (BDI), the Geriatric Depression Scale (GDS), and the Hamilton Rating Scale for Depression (HDRS-17) were used to evaluate levels of depression and mood disturbances. Additionally, the Apathy Evaluation Scale (AES-C) and the Snaith–Hamilton Pleasure Scale (SHAPS) were used to measure anhedonia, motivation, and emotional blunting, while the Clinical Global Impression (CGI) scale provided an overall assessment of treatment response.

For participants with ASD, various tools were employed to assess social responsiveness and behavioral symptoms. These included the Childhood Autism Rating Scale (CARS), the Autism Spectrum Quotient (AQ), the Australian Scale for Asperger's Syndrome (ASAS), and the Social Responsiveness Scale (SRS). These instruments allowed researchers to evaluate the impact of TPS on social behavior, communication skills, and other autism-related symptomatology.

In the context of ADHD, behavioral symptoms and hyperactivity levels were measured using the Swanson, Nolan, and Pelham Teacher and Parent Rating Scale (SNAP-IV) and the ADHD Rating Scale–IV (ADHD RS-IV). These scales were specifically designed to capture changes in attention and hyperactive-impulsive behavior, helping to determine the potential effects of TPS on this population.

For studies involving healthy participants, the assessment of perceived pain and perception of adverse effects was conducted using tools such as the Numeric Rating Scale (NRS). Additionally, the Two Point Orientation/Discrimination Task (2POD), and the Coin Rotation Task (CRT) were applied to observe TPS effects on task performance. Neuroimaging techniques, including fMRI, DTI, and EEG, were used extensively to evaluate changes in brain activity, connectivity, and structure following TPS.

By organizing the outcome measures according to their relevant populations, this approach allows for a more nuanced understanding of how TPS might differentially affect cognitive, motor, and mood-related functions across diverse groups.

Consortium to Establish a Registry for Alzheimer's Disease (CERAD)

CERAD is an umbrella term that refers to the standardized procedures for the evaluation and diagnosis of AD patients (Sotaniemi et al., 2012). The main CERAD instruments and ancillary materials consist of clinical, neuropsychological, neuropathological, and neuroimaging batteries, a behavior rating scale for dementia, family history and services assessment, autopsy resources, and educational brochures that provide information on early symptoms of AD. Some of the included studies in this review utilized the CERAD neuropsychological battery and reflected its results as CERAD total score (CTS). The neuropsychological battery consists of Verbal Fluency (animal naming, maximum score = 24), Boston Naming (15 items, maximum score 15), Mini-Mental State Examination (MMSE), Word List Learning (maximum score = 30), Constructional Praxis (maximum score = 11), Word List Recall (maximum score = 10), Word List Recognition (10 original words, 10 foils; maximum score = 10), and Constructional Praxis recall (Heyman,

2008). The CTS was calculated by summing the individual raw scores of subtests excluding the MMSE and corrected for age, gender, and formal education (Chandler et al., 2005; Rossetti et al., 2010).

Alzheimer's Disease Assessment Scale (ADAS)

The ADAS is a scale developed to evaluate the severity of cognitive and behavioral impairments in AD patients (Cavanna, 2023). It consists of 21 items with the inclusion of language comprehension, memory, orientation, visuospatial tasks (e.g., drawing figures), and physical tasks reflecting ideational praxis. The scoring range is from 0 to 70, with higher scores corresponding to more severe impairment. The cognitive part of the ADAS is abbreviated as ADAS-Cog, and compared to MMSE, it is more sensitive, reliable, and less influenced by a patient's education level and language skills. The behavioral part, on the other hand, measures mood, attention, delusions, and motor activity.

Montreal Cognitive Assessment (MoCA)

MoCA is a screening instrument to detect cognitive impairment. It assesses several cognitive domains such as attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The maximum score that a patient can get is 30, and higher scores refer to normal cognitive functioning (typically 26 or above, but different cutoff scores exist in different populations) (Nasreddine et al., 2005). The tasks include alternating trail making, visuoconstructional skills (drawing a cube or a clock), animal naming task, short-term memory recall, forward and backward digit span, sentence

repetition, verbal fluency, abstraction, delayed recall, and orientation. The Hong Kong Chinese version of MoCA is used in the included studies with Chinese participants (Yeung et al., 2014).

Mini-Mental State Examination (MMSE)

The MMSE (Folstein et al., 1975), is a questionnaire that consists of 11 questions with a total score of 30 points to assess cognitive impairment, commonly used to screen dementia (Arevalo-Rodriguez et al., 2021). It includes simple questions for evaluating several abilities: orientation to time and place, attention and calculation (such as counting or spelling backward), recall, language (i.e., object naming), repetition, and complex commands (e.g., drawing a figure).

Two Point Orientation/Discrimination Task (2POD)

The 2POD is a measure of tactile perception. It is used to evaluate a patient's ability to identify and discern two nearby objects touching the skin at two points, versus only one (Tong et al., 2013). The assessment relies on the difference in tactile receptor density in different parts of the body and somatosensory cortical representations. The therapist or researcher can use calipers or reshaped paper clips.

Coin Rotation Task (CRT)

The CRT is designed to assess an individual's psychomotor processing speed (Hill et al., 2010). During CRT, participants rotate a coin, by using thumb, index, and middle fingers, through consecutive 180-degree turns 20 times as rapidly as possible.

Stroop Test

The family of Stroop tests is used to measure selective attention, cognitive control, and response inhibition (Goldberg & Bougakov, 2005). The test is derived from the fact that it takes longer to name colors than reading words. During a typical version of a Stroop test, ink color naming (e.g., of non-word strings of letters), or non-color word reading could be used as baseline task, and naming the ink color of color words (e.g., blue written in red, or green written in green) as the experimental task. In the critical condition, it is harder to name the color (slower and more prone to errors) of words that indicate a different color (e.g., blue written in red) than the color of words whose meaning corresponds to their own ink color (blue written in blue), which are termed incompatible and compatible conditions, respectively.

The Lawton Instrumental Activities of Daily Living Scale (IADL)

The IADL is an instrument to measure a range of skills for self-care, and sustaining independent living (Graf, 2008). It evaluates eight domains of basic living skills, as follows: using a telephone, shopping, cooking, housekeeping, doing laundry, using transportation, taking medication, and handling finances. The score is either 0 or 1 for each question, with a maximum possible total of 8 points.

The Unified Parkinson's Disease Rating Scale (UPDRS-III)

The UPDRS is used for measuring the longitudinal course of impairment and disability caused by PD (Fish, 2011). It consists of six sections as follows: Part I: Mentation, mood, and behavior; Part II: Activities of daily life (ADL); Part III: Clinician-scored motor evaluation; Part IV: Complications of therapy; Part V: Modified Hoehn and Yahr Scale; Part VI: Schwab and

England ADL scale. In the included study by Osou and colleagues (2023), UPDRS Part III was utilized to monitor the motor functioning of PD patients. The UPDRS-III is scored on a 0 to 4 scale, and higher scores mean increased severity.

Neuropsychiatric Inventory (NPI)

The NPI is a measure of evaluating a range of behaviors in patients with neurodegenerative diseases (Cummings, 2009). It is used to identify ten behavioral areas: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, and aberrant motor behavior, and two neurovegetative areas (i.e., sleep dysregulations and dysregulated eating). The NPI is administered during an interview with the patient's caregiver. For the behavioral part of the NPI, there are measures: frequency, severity, total (frequency multiplied by severity), and caregiver's distress. The total NPI score is calculated by summing the points from the behavioral part, and the total distress score is calculated by adding scores of behavioral and neurovegetative items.

Childhood Autism Rating Scale (CARS)

The CARS is a frequently used scale to evaluate behavior for autism diagnosis (Ozonoff et al., 2005). It evaluates a child's behavior, characteristics, and abilities in comparison to the expected developmental growth. The scale evaluates fifteen items as follows: relationship to people, imitation, emotional response, body use, object use, adaptation to change, visual response, listening response, taste-smell-touch response and use, fear and nervousness, verbal communication, non-verbal communication, activity level, level and consistency of intellectual response, and general impressions. The rating is done by a primary caregiver, a teacher, or a

healthcare professional by scoring 1 to 4, with a maximum of 60. Higher scores indicate more severe autism.

Autism Spectrum Quotient (AQ)

The AQ is a scale consisting of fifty questions to assess the presence of ASD in adults (Baron-Cohen et al., 2001). It is mostly used in self-assessment format. AQ is designed in a way that approximately half of the questions elicit an "agree" and the other half a "disagree" response, and it assesses five domains associated with ASD: social skills, communication skills, imagination, attention to detail, attention switching, and tolerance of change. The AQ scoring range is from 0 to 50, with a score above 32 indicating clinical level of autistic traits.

Australian Scale for Asperger's Syndrome (ASAS)

The ASAS is developed to assess the likelihood of children at primary school age being at risk of developing Asperger's syndrome (Robinson, 2021). The scale is intended to be filled by parents, teachers, or professionals who know the child. It includes 24 questions of which answers are graded from 0 to 6 ("Rarely" to "Frequently"). The ASAS aims to measure social and emotional abilities, communication skills, cognitive skills, specific interests, and movement skills. Additionally, it also seeks information for identifying unusual fear or distress from specific stimuli, tendency to flap or rock in exciting or stressful situations, sensitivity to low levels of pain, speech acquisition age, and unusual facial expressions.

Social Responsiveness Scale (SRS)

The SRS is a parent or teacher questionnaire designed to assess the social abilities of children from 4 years to 18 years of age (Bölte et al., 2008). It comprises 65 items to evaluate children's behavior during the last six months, and responses are from "0" (not true) to "3" (almost always true). The possible maximum score is 195, and higher scores indicate more severe symptoms of autism.

The Swanson, Nolan, and Pelham Teacher and Parent Rating Scale (SNAP-IV)

The SNAP is a rating scale designed to evaluate the possibility of developing ADHD and oppositional defiant disorder (ODD) (Hall et al., 2020). Compared to the original version of SNAP which had 43 questions, the SNAP-IV consists of 26 items. It rates inattentive symptoms, hyperactivity/impulsivity symptoms, and combined ADHD-ODD symptoms. Symptom severity is measured based on a 4-point scale with a maximum score of 78: from "0" (not at all) to "3" (very much). The cutoff score for inattentive and hyperactivity subsets is 13 out of 27, and it is 8 out of 24 for comorbid ADHD-ODD subset. Higher scores reflect more severe symptoms.

The ADHD Rating Scale–IV (ADHD RS-IV)

ADHD RS-IV is a scale designed to obtain parent ratings of the frequency of ADHD symptoms in children and young adolescents in the last six months (DuPaul et al., 1998). It consists of 2 subscales with a total number of 18 questions: 9 items in the inattention subscale, and 9 items in the hyperactivity/impulsivity subscale. Responses are designed as a 4-point scale from "rarely or never" to "always or very often". Higher scores show more propensity of a child to develop ADHD, but this tool should not be considered alone for diagnosis.

The Clinical Global Impression (CGI)

The CGI is a brief 3-item scale administered by the observer to provide a summary of symptom changes in treatment studies (Busner & Targum, 2007). Its items allow clinicians to evaluate the severity of the patient's condition (CGI-S), the level of improvement after treatment (CGI-I), and the efficacy of treatment in terms of therapeutic and adverse effects (CGI-E). CGI-S and CGI-I are both a 7-point scale, and CGI-E is a 4x4 rating table comprised of therapeutic effects on the rows and adverse effects on columns.

Numeric Rating Scale (NRS)

The NRS is a simple 10-point scale that allows patients to rate perceived symptoms or side effects (Devin & McGirt, 2015). The scoring is also very simple. "0" represents no pain, and "10" represents extreme pain. During the treatment process, the observer collects scores at different time points and compares them over a time period. In the included studies in which NRS was utilized, it was used for rating the pain and adverse effects.

Beck Depression Inventory (BDI) and Geriatric Depression Scale (GDS)

The BDI and GDS are both self-report inventories to measure the severity of depressive symptoms. The current version of BDI is the BDI-II which contains 21 items, and it is designed for people aged 13 or older (Beck et al., 1996). It is developed to assess the severity of symptoms over time such as irritability, hopelessness, fatigue, feelings of worthlessness, loss of energy, and difficulties in concentration. Each answer is scored on a 4-point scale from "0" to "3", and the total score is calculated by summing the responses to a maximum of 63 (0-13: minimal depression, 14-19: mild depression, 20-28: moderate depression, 29-63: severe depression). In comparison to

BDI, the GDS is designed to assess depression in older adults, and its answers are based on a "Yes/No" format. The original version of CGS contained 30 items, and it was proven to be time-consuming as patients with depression feel fatigued and have difficulties concentrating. For this reason, a shortened version of GDS (GDS-S) was developed by selecting 15 items that are highly correlated with depressive symptoms (Van Marwijk et al., 1995). The total GDS-S score is obtained by summing 1 point for each positive response of 10 items and 1 point for each negative response of 5 items, with a maximum possible score of 15 points. A score of 5 or more suggests depression.

Hamilton rating scale for depression (HDRS-17)

The HDRS is designed to measure the severity of depressive symptoms of adults over the past week (Rajewska-Rager et al., 2023). Compared to BDI and GDS, the HDRS is clinician-administered. It evaluates depression by examining mood, guilt, suicidal ideation, insomnia, motor retardation and agitation, anxiety, appetite, weight loss, and somatic symptoms. On the HDRS-17 version, categories are defined based on scores, with a maximum of 52 points, as follows: 0-7: normal, 8-16: mild depression, 17-23: moderate depression, 24 and over: severe depression.

Snaith–Hamilton Pleasure Scale (SHAPS)

The SHAPS is a gold standard to measure to experience pleasure or the severity of anhedonia (Langvik & Borgen Austad, 2019). It consists of 14 items that cover domains of social interaction, food and drink, sensory experience, and interest/pastimes. The total score ranges from 0 to 14 with a cutoff score of 3 or more being considered abnormal.

Apathy Evaluation Scale (AES-C)

The AES-C is the clinical version of AES that was developed to measure apathy in adults and the elderly. It is comprised of 18 items to help the clinician to evaluate the emotional, behavioral, and cognitive aspects of apathy (Furneri et al., 2021). The responses are based on a 4-point scale as “not at all”, “slightly characteristic”, “somewhat characteristic”, and “a lot characteristic”. The scoring of AES-C ranges between 18 to 72, with higher scores indicating more apathy.

Pfeffer Functional Activities Questionnaire (P-FAQ)

The P-FAQ, developed by Pfeffer and colleagues in 1982, measures instrumental activities of daily living in older adults. It includes 10 items administered by an informant. Each question is scored 0 to 3, and the maximum score is 30. The cutoff score for P-FAQ is 9 (dependent on three or more activities) which indicates a patient is considered to have impaired functioning.

Zarit Caregiver Burden Interview

It is a self-report measure to rate the caregiver’s burden consisting of 22 items (Domínguez-Vergara et al., 2023). The responses are scored based on a 5-point scale from “0” (never) to “4” (almost always). The total score ranges from 0 to 88, with higher scores showing greater caregiver stress.

Neuroimaging Methods

A variety of neuroimaging methods were used in the included studies depending on the investigated research questions and target populations. Functional magnetic resonance imaging

(fMRI) is used to monitor resting-state (rsFC) and task-dependent functional connectivity, cortico-morphological changes, and network activity of different brain areas. DTI is utilized as a proxy to evaluate white matter micro-structural characteristics through measures such as fractional anisotropy, axial and radial diffusivity in addition to mean diffusivity. Finally, electroencephalography (EEG) was used to measure SEP.

2.3. Risk of Bias Assessment

After the full-text screening of the included studies, a risk of bias assessment was conducted independently for each study to evaluate their methodological quality and identify any potential sources of bias. This assessment ensures that the studies included in the review meet the necessary standards of validity and reliability, thereby enhancing the robustness of the findings and the credibility of the conclusions drawn from the review. The instruments were selected in accordance with the study design (See Appendix 2 for quality assessment tools).

2.3.1. Quality Appraisal Tools

2.3.1.1. NIH Quality Assessment of Controlled Intervention Studies

This checklist was developed by the US National Heart Lung and Blood Institute (NHLBI) in 2014 to assess the risk of bias for randomized control trials (RCTs). It consists of 14 items with "Yes/No" responses to evaluate the quality of internal validity. The quality ratings are "Good", "Fair", or "Poor". Scoring is defined as 1 point for each "Yes" and 0 for each "No", with a possible total score of 14, and the cutoff score of good quality is determined as 11 points for this review.

2.3.1.2. NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group

For the uncontrolled before-after studies included in this review, the risk of bias was assessed by utilizing the checklist developed by NHLBI in 2014. It is formed of 12 Yes/No questions, with quality ratings of "Good", "Fair", or "Poor". The scoring strategy was determined by assigning 1 point for each item rated "Yes", resulting in a maximum possible score of 12 points, and the categories are defined as follows: 0-4: poor, 5-8: fair, and 9-12: good.

2.4. Data Synthesis and Analysis

Considering the heterogeneity and paucity of included studies, performing a meta-analysis was not possible (Deeks et al., 2023). The included studies were grouped according to the target population for a clearer comparison of results. Moreover, the adverse effects reported in individual studies were summarized.

2.4.1. Narrative Synthesis

The narrative synthesis will provide a structured summary and interpretation of the findings from the included studies, organized into three main outcome domains: (1) Neuropsychological outcomes, (2) Neuroimaging outcomes, and (3) Improvements in behavioral symptoms, social functioning, and daily life. This approach will enable a comprehensive assessment of the neuromodulatory effects of TPS across multiple dimensions, highlighting patterns, trends, and gaps in the existing literature.

2.4.1.1. Neuropsychological Outcomes

The first part of the synthesis will focus on the neuropsychological outcomes reported in the included studies. This section will explore the effects of TPS on various cognitive domains such as memory, attention, executive function, language, and processing speed, as assessed by standardized neuropsychological tests (e.g., MMSE, MoCA, Stroop Test, Trail Making Test (TMT)), as well as improvements in motor functioning. The synthesis will compare and contrast the findings across different populations, including those with AD, NCD, MDD, PD, and healthy participants. The methodological quality of the studies, sample characteristics, and the specific TPS parameters (e.g., energy flux density, duration, frequency) will be considered to identify any patterns in neuropsychological effects. Differences in cognitive outcomes between RCTs and nonrandomized studies will also be highlighted, providing insights into the robustness of the evidence.

2.4.1.2. Neuroimaging Outcomes

The second part of the synthesis will examine neuroimaging outcomes, focusing on the brain's structural and functional changes associated with TPS. Studies utilizing various imaging modalities, such as fMRI, DTI, and EEG, will be included in this section. The synthesis will describe changes in brain connectivity, cortical thickness, gray and white matter volume, and functional network organization, as measured by techniques such as resting-state functional connectivity, surface-based morphometry, and graph analysis. This part will also compare findings across different populations and TPS parameters to determine how TPS may modulate specific brain regions and networks. Additionally, the synthesis will address the relationship between

neuroimaging changes and clinical or neuropsychological outcomes, providing a deeper understanding of the neural mechanisms underlying TPS effects.

2.4.1.3. Improvements in Behavioral Symptoms, Social Functioning, and Daily Life

The third part of the synthesis will focus on the impact of TPS on behavioral symptoms, social functioning, and daily life activities, as reported in the included studies. This section will explore changes in symptoms related to mood (e.g., BDI and GDS), social behavior, and the ability to perform daily activities (e.g., IADL, CGI, and AES-C). The synthesis will compare outcomes across different conditions, such as ASD, MDD, PD, and AD, to identify commonalities and differences in TPS effects.

Additionally, any reported adverse effects or safety concerns associated with TPS will also be integrated into this section, providing a comprehensive overview of its impact on patients' overall well-being and quality of life.

A narrative synthesis approach was chosen due to the heterogeneity of study designs, populations, and outcomes in the included studies. The findings will be synthesized by grouping similar studies within each of the three outcome domains, identifying patterns and relationships among the results, and exploring potential sources of variability or inconsistency. The narrative synthesis will provide a comprehensive interpretation of the current evidence, highlighting key findings, methodological limitations, and areas for future research.

3. Results

3.1. Study Selection

Figure 4 shows the flow diagram of the study selection process. A total number of 124 studies were initially identified from the databases (n = 121), and registries (n =3). Duplicates were removed before screening (n = 88). Thirty-six articles were screened, and 4 of them were removed before full-text retrieval due to being a review article and missing data. Thirty-two articles were retrieved for full-text investigation. Then, seventeen articles were removed in accordance with the exclusion criteria: including additional interventions (n = 5), study protocols (n = 3), computational study (n = 1), conference poster (n = 2), scientific letter (n = 2), case report (n = 2), and meeting abstract (n = 2). Ultimately, a total number of 15 studies were included in this review.

3.2. Characteristics of Included Studies

A total number of 15 studies were included in this review. The characteristics of the included studies are shown in Table 1.

3.2.1. Study Design

Among the fifteen included studies, ten of them were open-label trials without a control group. The data collected in these noncomparative studies was recorded before and after the TPS intervention. One of the included studies was conducted by using a single-blind, randomized design with a waitlist control (WC) group (Cheung et al., 2023b). In this study, participants were divided into two groups: TPS intervention vs WC groups, and the comparison of the effect was carried out between participants in the TPS group and those who did not receive the treatment at the same time. Finally, the remaining four studies were double-blind, sham-controlled RCTs.

Figure 4

PRISMA Flow Diagram of Study Inclusion for This Systematic Review

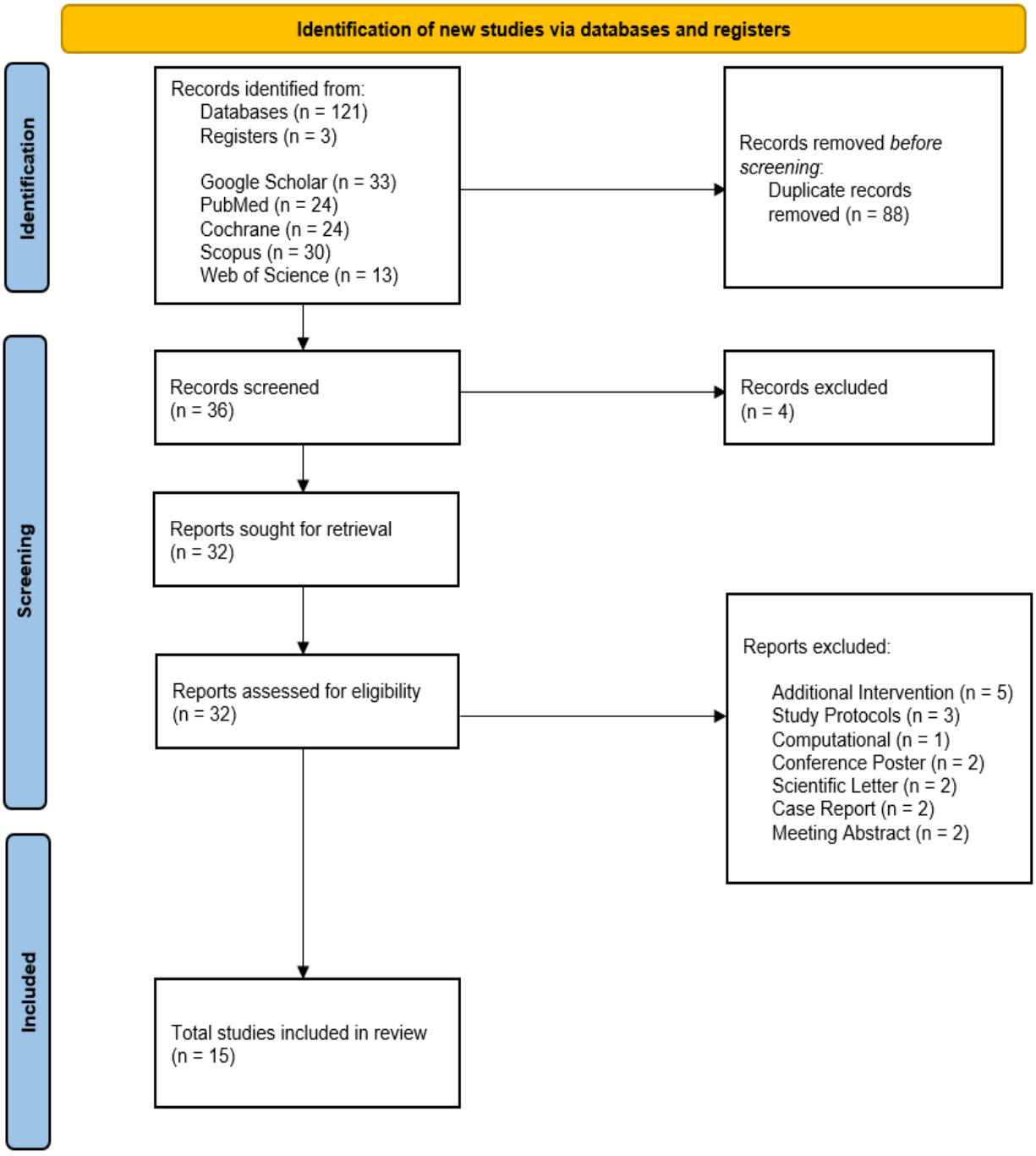


Table 1

Study Characteristics and Outcome Measures of the Included Studies

Study	Study Design	Subjects	Outcome Measures
Beisteiner et al. (2020)	Uncontrolled Open Label	35 AD Patients	CERAD total score (CTS), CERAD logistic regression score (LR), CERAD principal component analysis (PCA) fMRI, Geriatric Depression Scale (GDS), Beck Depression Inventory (BDI)
Popescu et al (2021)	Uncontrolled Open Label	17 AD Patients	CERAD Total Score (CTS), fMRI (surface-based morphometry on FreeSurfer)
Dörl et al. (2022)	Uncontrolled Open Label	18 AD Patients	CERAD total score (CTS), CERAD principal component analysis (PCA) fMRI
Novak et al. (2022)	Uncontrolled Open Label	6 AD Patients	CERAD
Cont et al. (2022)	Uncontrolled Open Label	11 AD patients	Alzheimer's Disease Assessment Scale (ADAS), Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Numeric rating scale (NRS)
Shinzato et al., (2024)	Uncontrolled Open Label	10 AD patients	ADAS - Cognitive Scale (ADAS-Cog), Neuropsychiatric Inventory (NPI), Pfeffer Functional Activities Questionnaire (P-FAQ), Zarit Caregiver Burden interview
Sprick (2022)	Uncontrolled Open Label	21 AD patients	Stroop-test Beck Depression Inventory (BDI)

Matt et al. (2022b)	Uncontrolled Open Label	18 AD patients	fMRI Beck Depression Inventory (BDI-II)
Matt et al. (2022a)	Randomized Sham-controlled Double-blind	20 Healthy Male Participants	2-point orientation/discrimination task (2POD) Coin rotation task (CRT) fMRI Diffusion Tensor Imaging (DTI)
Matt et al. (2020)	Randomized Sham-controlled Single-blind	10 Healthy Male Participants	EEG - somatosensory evoked potentials (SEPs)
Cheung et al. (2023b)	Randomized Waitlist Control Single-blind	30 Adults with MDD	Hamilton rating scale for depression (HDRS-17), Snaith–Hamilton pleasure scale (SHAPS), Lawton instrumental activities of daily living scale (IADL), MoCA, fMRI
Cheung et al. (2023a)	Randomized Sham-controlled Double-blind	32 Participants ASD	Childhood Autism Rating Scale (CARS), Autism Spectrum Quotient (AQ), Australian Scale for Asperger's Syndrome (ASAS), Social Responsiveness Scale (SRS), Trail Making Test (TMT), Verbal Fluency Test (VFT), Stroop test, Digit Span Test, Clinical Global Impression Scale (CGI)

Fong et al (2023)	Uncontrolled Open Label	19 NCD Patients	The Hong Kong Chinese version of MoCA, Forward and backward digit span (DS), Stroop test, Verbal Fluency Test (VFT), Trail Making Test (TMT), Lawton Instrumental Activities of Daily Living Scale (Chinese IADL), Hamilton rating scale for depression (HDRS-17), Apathy Evaluation Scale (AES-C)
Osou (2023)	Uncontrolled Open Label	20 PD Patients	Unified Parkinson's Disease Rating Scale part III (UPDRS-III)
Cheung et al., (2024)	Randomized Sham-controlled Double-blind	32 Adolescents with ADHD	The Swanson, Nolan, and Pelham Teacher and Parent Rating Scale (SNAP-IV), The Clinical Global Impression Severity (CGI-S), The Clinical Global Impression Improvement (CGI-I), Stroop test, The ADHD Rating Scale–IV (ADHD RS-IV)

3.2.2. Participants

A total number of 299 participants were recruited in the included studies. Among these participants, there were 136 AD, 30 MDD, 32 ASD, 19 NCD, 20 PD, 32 ADHD patients, and 30 healthy participants. The age range of AD patients was 50 to 84. The mean age could not be calculated, because some of the included studies with AD patients did not provide the mean age of their participants. Similarly, two of the included studies with AD patients also did not provide gender distribution of their participants (Novak et al., 2022, n = 6; Sprick & Köhne, 2021, n = 21).

Of the remaining 109 AD patients, 63 were female and 46 were male. Cheung and colleagues (2023b) recruited a total number of 30 MDD patients consisting of 22 females and 8 males, and their mean age was 36.5 years. In another study by Cheung and colleagues (2023a), 32 adolescents diagnosed with ASD were recruited. Amongst, there were 27 males and 5 females, and their mean age was 13.1 years. In their latest study, Cheung and colleagues (2024) used TPS intervention on adolescents with ADHD. A total of 32 participants, 25 male and 7 female, with an average age of 13.1, were included in this study. In their TPS study, Fong and colleagues (2023) recruited 19 mild NCD patients with a mean age of 74.3, 7 male and 12 female. As the last patient group in the included studies, 20 PD patients, which comprised 15 males and 5 females, participated in the study conducted by Osou and colleagues (2023). The mean age of the PD patients was 67.6 years.

In the case of studies involving healthy participants, Matt and colleagues (2020) recruited 10 healthy male participants with a mean age of 30.9 years old for their study in which authors examined the efficacy of the number of TPS pulses. In another study conducted by Matt and colleagues (2022a), 20 healthy male participants took part in their study. Their mean age was 26.5 years.

3.2.3. Intervention Details

TPS is one of the most recent NIBS techniques that received CE approval in 2018. The TPS system used in the included studies was developed by NEUROLITH, Storz Medical AG, Tägerwilen, Switzerland. It consists of a mobile TPS transducer and an infrared camera system for neuronavigation.

According to Beisteiner and colleagues (2020), the limitations of the TPS system were defined based on unpublished experiments for dose finding and CE approval as follows: maximum energy flux density: 0.25 mJ/mm^2 at 4 Hz, maximum number of pulses per treatment: 6000, and maximum peak pressure 25 MPa. Additionally, the authors claimed that those unpublished results revealed no tissue lesions below 40 MPa during the trials.

In light of these limitations, the stimulation parameters were highly consistent in the included studies with a small variability. Targeted brain regions and TPS stimulation parameters of the included studies are demonstrated in Table 2.

Table 2

Intervention Details of the Included Studies

Study	TPS Parameters	Duration	Stimulation Target
Beisteiner et al. (2020)	3 µs, 0.2 mJ/mm2 energy flux density, Pulse repetition frequency: 5 Hz, Pulses per session: 6000	2–4 weeks (center 1), 2 weeks (center 2)	• Bilateral frontal cortex, • Bilateral lateral parietal cortex, •Extended precuneus cortex (center 1) • Global Cortical Stimulation (center 2)
Popescu et al (2021)	3 µs, 0.2 mJ/mm2 energy flux density, Pulse repetition frequency: 5 Hz, Pulses per session: 6000	13 Pts: 4 weeks 3 Pts: 2 weeks 1 Pts: 3 weeks	• Bilateral frontal cortex (dorsolateral prefrontal cortex and inferior frontal cortex extending to Broca's area) • Bilateral lateral parietal cortex (extending to Wernicke's area) • Extended precuneus cortex
Dörl et al. (2022)	3 µs, 0.2 mJ/mm2 energy flux density, Pulse repetition frequency: 5 Hz, Pulses per session: 6000	14 Pts: 4 weeks 3 Pts: 2 weeks 1 Pts: 3 weeks (3 sessions per week)	• Bilateral frontal cortex, • Bilateral lateral parietal cortex, • Extended precuneus cortex, • Bilateral temporal cortex

Novak et al. (2022)	3 µs, 0.2 mJ/mm2 energy flux density, Pulse repetition frequency: 5 Hz, Pulses per session: 6000	6 Sessions within 2 weeks 1 re-treatment session/month after 3-months follow-up 2nd booster treatment (6 sessions) after 2 years	• Bilateral frontal cortex, • Bilateral lateral parietal cortex, • Extended precuneus cortex, • Bilateral temporal cortex
Cont et al. (2022)	0.2 mJ/mm2 energy flux density, Pulse repetition frequency: 4 Hz, Pulses per session: 3000 or 6000	2 weeks (6 sessions-6000 pulses) or 2 weeks (12 sessions - 3000 pulses)	• Bilateral frontal cortex, • Bilateral lateral parietal cortex, • Extended precuneus cortex, • Bilateral temporal cortex
Shinzato et al., (2024)	0.25 mJ/mm2 energy flux density, Pulse repetition frequency: 4 Hz, Pulses per session: 6000	5 Weeks, 2 sessions per week	• Frontotemporal Region, • Parietal Lobe, • Occipital lobes
Sprick & Köhne (2022)	3 µs, 0.25 mJ/mm2 energy flux density, Pulse repetition frequency: 4 Hz, Pulses per session: 3000	2 weeks	• Bilateral dorsolateral prefrontal cortex • Bilateral parietal lobe • Bilateral temporal lobe
Matt et al. (2022b)	3 µs, 0.2 mJ/mm2 energy flux density, Pulse repetition frequency: 5 Hz, Pulses per session: 6000	14 Pts: 4 weeks 3 Pts: 2 weeks 1 Pts: 3 weeks (3 sessions per week)	• Bilateral frontal cortex, • Bilateral lateral parietal cortex, • Extended precuneus cortex, • Bilateral temporal cortex
Matt et al. (2022a)	3 µs Energy flux density = 0.25 mJ/mm2 Pulse repetition frequency: 4 Hz, Pulses per session: 1000	7 weeks (3 weeks of each session, 1 week of pause between sessions) Session Duration: 4 minutes	• The Left Postcentral Gyrus
Matt et al. (2020)	3 µs, 0.25 mJ/mm2 energy flux density, Pulse repetition	1 session	• The Left Postcentral Gyrus

	frequency: 4 Hz, Pulses per session: 10/100/1000		
Cheung et al. (2023b)	3 μs, 0.2 - 0.25 mJ/mm2 energy flux density, Pulse repetition frequency: 3 - 4 Hz, Pulses per session: 300	2 weeks, (3 sessions per week) Session Duration: 30 minutes	• Left Dorsolateral Prefrontal Cortex (dlPFC)
Cheung et al. (2023a)	3 μs, 0.2 - 0.25 mJ/mm2 energy flux density, Pulse repetition frequency: 2 - 4 Hz, Pulses per session: 800	2 weeks, (3 sessions per week) Session Duration: 30 minutes	• Right Temporoparietal Junction (rTPJ)
Fong et al (2023)	3 μs, 0.2 - 0.25 mJ/mm2 energy flux density, Pulse repetition frequency: 4 - 5 Hz, Pulses per session: 6000	2 weeks, (3 sessions per week) Session Duration: 30 minutes	Global brain stimulation approach (frontal, parietal, temporal, and occipital lobes)
Osou (2023)	3 μs, 0.25 mJ/mm2 energy flux density, Pulse repetition frequency: 4 Hz, Pulses per session: 4000	2 weeks 10 sessions, (5 sessions each week)	• Primary Sensorimotor Area, • Supplementary Motor Area, • Cingulate Motor Area, • Left Dorsolateral Prefrontal Cortex (dlPFC)
Cheung et al., (2024)	3 μs, 0.25 mJ/mm2 energy flux density, Pulse repetition frequency: 4 Hz, Pulses per session: 800	2 weeks, (3 sessions per week) Session Duration: 30 minutes	• Left Dorsolateral Prefrontal Cortex (dlPFC)

3.2.4. Outcome Measures

To quantify the effectiveness of TPS, the included studies in this review utilized a variety of outcome measures respectively, neuropsychological outcomes, neuroimaging methods, and

behavioral assessments such as mood changes, improvements in depressive symptoms, social and daily life, and their correlations with each other.

To begin with the primary neuropsychological outcomes, the CTS (Beisteiner et al., 2020; Dörl et al., 2022; Novak et al., 2022; Popescu et al., 2021) and ADAS-Cog (Cont et al., 2022; Shinzato et al., 2024) were the major outcome measures in studies with AD patients to evaluate cognitive improvements resulted from TPS intervention. In their study with AD patients, Sprick & Köhne (2022) utilized the Stroop Test to monitor the improvements in executive functions. In another study with older adults, Fong and colleagues (2023) employed the Hong Kong Chinese version of MoCA as the primary outcome measure to assess the global cognition of patients with NCD. Moreover, Osou and colleagues (2023) used UPDRS-III to measure improvements in motor symptoms of PD patients. In addition to studies with older adults in this review, Cheung and colleagues (2023a) utilized CARS to observe TPS effectiveness on ASD symptoms. Lastly, Matt and colleagues (2022a) used the 2POD to set the tactile spatial discrimination threshold, and the CRT to evaluate manual dexterity and sensorimotor processing.

In terms of the primary neuroimaging outcomes, Matt and colleagues (2022b) employed fMRI to monitor alterations in network activity related to AD and depression, and functional connectivity after TPS intervention. Moreover, the authors investigated the correlation between functional connectivity changes and improvements in depressive symptoms. Similarly, in their other study, Matt and colleagues (2022a) also used fMRI to evaluate changes in rsFC in primary and secondary somatosensory networks of healthy participants. Lastly in their pilot study, Matt

and colleagues (2020) utilized EEG to observe the effects of number of the pulses on SEPs in healthy participants.

In respect of behavioral assessments as the primary outcome, Cheung and colleagues (2023b) used HDRS-17 to inspect improvements in depressive symptoms and mood changes in adults with MDD. Additionally, Sprick & Köhne (2022) used BDI to assess their participants' depressive symptoms besides executive functions. Lastly, the SNAP-IV was used to assess inattention, hyperactivity/impulsivity, and oppositional defiance in adolescents with ADHD (Cheung et al., 2024).

The secondary outcomes of the included studies in this review also vary in line with primary outcomes. First of all, CERAD logistic regression (CERAD-LR) and CERAD principal component analysis (CERAD-PCA) were used in the study conducted by Beisteiner and colleagues (2020). The CERAD-LR was generated by using z-transformed scores of CERAD subtests that specifically point out AD-type dementia. The CERAD-PCA was used in two of the included studies, and it was generated by using the same method as CERAD-LR (Beisteiner et al., 2020; Dörl et al., 2022). The CERAD-PCA was particularly useful as it allowed researchers to evaluate memory, verbal processing, and visuospatial processing separately. In addition to CERAD-LR and PCA, several other secondary measurements were used to monitor cognitive dysfunction and improvements in the included studies. These measurements are as follows: MoCA (Cheung et al., 2023b; Cont et al., 2022), MMSE (Cont et al., 2022). Moreover, Cheung and colleagues (2023a) utilized a variety of secondary outcomes to observe alterations in cognitive and executive functions: the AQ, TMT, verbal fluency (VFT), digit span, and Stroop tests. Similarly,

Fong and colleagues (2023) also used several secondary neuropsychological outcomes: Forward and backward digit span, Stroop test, TMT, and VFT. Regarding the neuroimaging methods, fMRI results were assessed as secondary outcomes in several studies: rsFC (Beisteiner et al., 2020), surface-based morphometry to examine changes in cortical thickness (Popescu et al., 2021), and graph analysis of a visuo-constructive network (Dörl et al., 2022). Furthermore, several additional outcome measures were used in the included studies to monitor behavioral and mood changes, improvements in depressive symptoms, and improvements in social and daily life. These outcome measures are as follows: the BDI (Beisteiner et al., 2020; Dörl et al., 2022), the GDS (Beisteiner et al., 2020; Dörl et al., 2022), and the HDRS-17 (Fong et al., 2023) for depressive symptoms and mood changes, the NRS to rate pain and side effects (Cont et al., 2022), the NPI (Shinzato et al., 2024), the SHAPS (Cheung et al., 2023b), the ASAS, the SRS, the CGI (Cheung et al., 2023a; Cheung et al., 2024) and the ADHD RS-IV (Cheung et al., 2024). In addition to behavioral assessments, measurements to evaluate improvements in participants' social and daily functioning were employed as follows: Zarit Caregiver Burden interview and P-FAQ (Shinzato et al., 2024), IADL (Cheung et al., 2023b), Chinese version of IADL (Fong et al., 2023) and AES-C (Fong et al., 2023). Lastly, Fong and colleagues (2023) also analyzed their participants' blood samples to examine changes in APOE gene status and BDNF serum concentration before and after TPS intervention.

3.3. Risk of Bias Assessment

Risk of bias results were grouped according to the study design of the included studies: Pre-Post and RCTS.

As mentioned above, the NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group (National Institutes of Health, 2014) was utilized for uncontrolled non-randomized studies, and the results were reported in Table 3. Among the ten non-randomized studies, two studies were rated as “Good”, seven studies rated as "Fair”, and one study was rated as "Poor” quality. To begin with, none of these studies reported blinding of outcome assessors. Secondly, sample sizes were evaluated according to the inclusion of neuroimaging methods, considering the cost of conducting fMRI and DTI studies (Crosson et al., 2010). Moreover, there has been an ongoing debate on the sufficient number of participants in an fMRI study. It has been argued that sample sizes of 50 or larger would be sufficient to have an acceptable level of power (Yarkoni, 2009). On the other hand, Pajula and Tohka (2016) performed an inter-subject correlation (ISC) analysis to define a reliable sample size and concluded that “Our findings suggested that with 20 subjects, on average, the ISC statistics had converged close to a large sample ISC statistic with 130 subjects” (p. 1). In light of these arguments, the sample sizes of the included non-randomized studies with fMRI and DTI were rated as “CD” (cannot determine) if the number is around 20 (+/- 5), and “insufficient” if less than that. Only the study by Beisteiner and colleagues (2020) was evaluated as having a sufficient sample size due to the number of participants (n = 35). Furthermore, the one study, which was qualified as “Poor”, rated in this way because of the following characteristics: eligibility criteria not explained, too small sample size, undescribed outcome measures, and statistical analyses. Lastly, three other studies in this category were evaluated as insufficient in terms of sample size as their results were based on standardized outcome measures rather than neuroimaging results.

To evaluate the risk of bias of the included RCTs in this review, the Quality Assessment of Controlled Intervention Studies was used (National Heart, Lung, and Blood Institute, 2014). The detail of the scoring is demonstrated in Table 4. A total number of 5 RCTs are included in this review. Among them, only the study by Matt and colleagues (2020) was rated as "Fair" due to several reasons as follows: randomization adequacy, blinding of assessors, overall and differential drop rates, and prespecified outcomes were not reported in the paper. Additionally, blinding of participants and power calculation were also not performed. The risk of bias of the four remaining RCTs was evaluated as "Good". Two studies were rated sufficient in all categories, and received full points of 14 (Cheung et al., 2023a; Cheung et al., 2024). The remaining two studies resulted in achieving 12 points for risk of bias assessment. Firstly, power calculation was not performed, and intention-to-treat analysis was not applicable to the study by Matt and colleagues (2022a). Similarly, Cheung and colleagues (2023b) did also not execute power calculation. The authors stated that there was not a sufficient number of examples to compare their estimated sample size, and for this reason, they decided to reference the number of participants to the study by Beistenier and colleagues (2020). Moreover, the authors did not report blinding of assessors.

In summary, the included nonrandomized studies were mostly assessed as "Fair" due to not reported blinding of outcome assessors, unperformed description of outcome measures, and sample sizes related to the inclusion of neuroimaging techniques or utilization of standardized tests. On the contrary, the included RCTs are mostly rated as "Good" with only some of them missing a few numbers of points due to reasons that would not lower the quality of the studies.

Table 3

Evaluation of selected publications according to the NIH quality assessment tool for pre-post studies with no control group

		Beisteiner et al., (2020)	Popescu et al., (2021)	Dörl et al., (2022)	Novak et al., (2022)	Cont et al., (2022)	Shinzato et al., (2024)	Sprick & Köhne, (2022)	Matt et al., (2022b)	Fong et al., (2023)	Osou et al. (2023)
Item 1	Study question	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Item 2	Eligibility criteria and study population	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Item 3	Study participants representative of clinical populations of interest	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Item 4	All eligible participants enrolled	Yes	No	Yes	CD	Yes	Yes	Yes	No	No	CD
Item 5	Sample size	Yes	CD	CD	No	No	No	CD	CD	CD	No
Item 6	Intervention clearly described	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Item 7	Outcome measurement clearly described, valid, and reliable	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Item 8	Blinding of outcome assessors	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Item 9	Follow-up rate	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Item 10	Statistical analysis	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes
Item 11	Multiple outcome measures	Yes	No	No	NR	No	Yes	No	No	No	No
Item 12	Group-level interventions and individual-level outcome efforts	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total Scores		10	7	7	3	8	9	8	7	7	6
Overall Rating		Good	Fair	Fair	Poor	Fair	Good	Fair	Fair	Fair	Fair

CD: cannot determine; NA: not applicable; NR: not reported

Table 4

Evaluation of selected publications according to the NIH quality assessment tool for controlled intervention studies

		Matt et al., (2020)	Matt et al., (2022a)	Cheung et al., (2023a)	Cheung et al., (2023b)	Cheung et al., (2024)
Item 1	Described as randomized	Yes	Yes	Yes	Yes	Yes
Item 2	Randomization adequacy	NR	Yes	Yes	Yes	Yes
Item 3	Concealed treatment allocation	Yes	Yes	Yes	Yes	Yes
Item 4	Blinding of participants	No	Yes	Yes	Yes	Yes
Item 5	Blinding of assessors	NR	Yes	Yes	NR	Yes
Item 6	Similarity of groups at baseline	Yes	Yes	Yes	Yes	Yes
Item 7	Overall drop-out rate	NR	Yes	Yes	Yes	Yes
Item 8	Differential drop-out rate between groups	NR	Yes	Yes	Yes	Yes
Item 9	Adherence to intervention protocols	Yes	Yes	Yes	Yes	Yes
Item 10	Avoidance of other interventions	Yes	Yes	Yes	Yes	Yes
Item 11	Outcome measures assessment	Yes	Yes	Yes	Yes	Yes
Item 12	Power calculation	No	No	Yes	No	Yes
Item 13	Prespecified outcomes	NR	Yes	Yes	Yes	Yes
Item 14	Intention-to-treat analysis	NA	NA	Yes	Yes	Yes
Total Score		6	12	14	12	14
Overall Rating		Fair	Good	Good	Good	Good

CD: cannot determine; NA: not applicable; NR: not reported

3.4. Findings of Individual Studies

As outlined in the narrative synthesis of the methods section, the findings of the included studies will be interpreted in three domains as Neuropsychological outcomes, Neuroimaging outcomes, and Improvements in behavioral symptoms, social functioning, and daily life, and therefore, the individual results will also be reported following the same order, if applicable.

3.4.1. Effectiveness of Neuronavigated TPS

Beisteiner and colleagues (2020) conducted the first pilot study involving 35 AD patients recruited from two centers, namely in Vienna, Austria (n = 19, 12 female) and in Bad Krozingen,

Germany (n = 16, 8 female). To evaluate the effectiveness of TPS on neuropsychological improvements in AD, the researchers used CTS and performed a mixed ANOVA. The analysis included two factors: time points (pre-stimulation, post-stimulation, 1-month, and 3-month follow-ups (FU)) and center (Vienna and Bad Krozingen). The results demonstrated a significant within-subject effect of time on CTS scores ($p < .0001$), indicating cognitive improvements across the different time points. Post-hoc comparisons further revealed significant cognitive improvements from baseline to post-stimulation ($p_{Bonf} < .0001$), baseline to 1-month FU ($p_{Bonf} < .0001$), and baseline to 3-month FU ($p_{Bonf} < .0001$), indicating sustained neuropsychological benefits of TPS over time. In comparison, the between-subjects effect of the center was not statistically significant ($p = .313$), suggesting no significant difference in outcomes between the two recruitment sites. Additionally, the authors also employed two additional analytic methods: CERAD-LR, which focuses on cognitive tests relevant to AD-type dementia, and CERAD-PCA, which allows for separate monitoring of memory, verbal processing, and visuospatial processing. For the CERAD-LR scores, a significant within-subject effect of time was observed ($p < .0001$), suggesting substantial cognitive improvement over the course of the study. Post-hoc pairwise comparisons showed significant enhancements in cognitive performance from baseline to post-stimulation ($p_{Bonf} < .0001$), baseline to 1-month FU ($p_{Bonf} < .0001$), and baseline to 3-months FU ($p_{Bonf} < .0001$). Additionally, there was a significant difference between post-stimulation and the 1-month FU ($p_{Bonf} = .012$), indicating continued improvement following treatment. These findings suggest that TPS treatment leads to significant improvements in AD-related dementia symptoms, with sustained benefits observed over a three-month period. Moreover, CERAD-PCA identified three factors that had eigenvalues greater than 1, namely MEMORY accounted for 46.25% of the total variance (including delayed recall and recognition of the Word List and on Savings of the Word

List and the Figures), VERBAL explained 13.95% of the variance(including the Verbal Fluency tasks and the Word List Total score), and FIGURAL elucidated 10.77% of the variance (including tasks related to visuospatial processing). Similarly, a mixed ANOVA was used with factors of time and center to demonstrate changes in each PCA factor. A significant within-subject effect, on the other hand, was found for all three PCA components (MEMORY, $p < .0001$; VERBAL, $p < .0001$; FIGURAL, $p = .014$). A significant and steady improvement over time was found in MEMORY and VERBAL factors, while a steady decline in the FIGURAL component was revealed. Authors stated that the decline in FIGURAL occurred because participants from center 1 did not receive TPS over the occipito-parietal cortex which is an important brain region involved in visuospatial processing. However, this difference in their results points out specific TPS effects on stimulated networks. In terms of depressive symptoms, the Wilcoxon Test revealed significant improvements in the GDS (baseline > 3 months FU ($p_{Bonf} = .012$)), and BDI (baseline > post-stim ($p_{Bonf} = .012$), baseline > 1month FU ($p_{Bonf} = .006$) and baseline > 3 months FU ($p_{Bonf} = .012$)). Additionally, the authors carried out a correlation analysis to investigate if improvements in CERAD and its subtests were associated with changes in depressive symptoms. It was shown that there were no significant correlations. Furthermore, fMRI results of a subgroup of participants (n = 18) revealed increased rsFC in the hippocampus, parahippocampal cortex, parietal cortex, and precuneus, indicating that TPS intervention led to a significant upregulation of the memory network. Additionally, fMRI data obtained during a face-name encoding task showed increased functional activation in the bilateral hippocampus after TPS. Moreover, the results revealed that significant correlations were found between increased activity and functional connectivity of the memory network with CTS ($r = .525$, $p = .001$), CERAD-LR ($r = .550$, $p = .001$), and MEMORY component of CERAD-PCA ($r = .450$, $p = .009$). In light of the results, the authors concluded that correlations between the memory

network and CTS, CERAD-LR, and MEMORY component suggest that memory network upregulation is linked to cognitive performance in this neurological condition.

Subsequently, Dörl and colleagues (2022) conducted a follow-up study with fMRI data from 18 AD patients (11 female) to assess the effectiveness of TPS on the Visuo-constructive Network. The network involved several posterior and parietal brain areas, including the bilateral angular gyrus (AG), intracalcarine cortex, posterior medial temporal gyrus, posterior cingulate cortex, and temporo-occipital fusiform cortex. The authors compared the FIGURAL factor of the CERAD-PCA before and after TPS intervention, finding a trend toward declining visuo-constructive capabilities ($p = .055$), which became significant at 3-months FU ($p = .007$). Additionally, a graph analysis revealed a significant reduction in global efficiency within the visuo-constructive network ($p = .016$), with a specific decline observed in the right AG (p-FDR = .015, corrected for multiple comparisons). A positive correlation was found between CERAD FIGURAL test scores and global efficiency values in the right AG ($p = 0.046$), indicating a joint decrease in both variables. The authors did not include the precuneus in the correlation analysis at the beginning, because only some parts of the precuneus belong to the visuo-constructive network. However, the analysis showed that even after including the stimulated precuneus area, the decline in network connectivity remained significant, which confirms a robust reduction in global efficiency in the right AG (p-FDR = 0.0262). These results also strengthen the findings of specific TPS effect on stimulated networks by Beisteiner et al (2020).

Similarly, Popescu and colleagues (2021) also conducted a follow-up study analyzing fMRI data from 17 patients with mild AD before and after TPS treatment. The authors assessed

cognitive improvements using the CTS and employed a surface-based morphometry approach to examine anatomical brain changes. They also conducted correlation analyses to explore the relationship between pre-to-post changes in CTS and cortical thickness in specific brain regions associated with AD, including the entorhinal, parahippocampal, lateral parietal (inferior and superior), and precuneus areas. The results demonstrated a significant improvement in CTS scores before and after TPS treatment (mean change = 3.76 ± 5.35, t [16] = 2.89, p = .01). However, no significant group-level differences were observed at the whole-brain level after correcting for multiple comparisons (FWE correction). Also, the results revealed significant correlations between changes in CTS scores and cortical thickness in the left superior parietal lobule (r = 0.70, p = .0017) and left precuneus (r = 0.39, p = .03). After adjusting for multiple comparisons, only the correlation for the left superior parietal lobule remained significant. These results persisted even after accounting for age-related variations in gray matter thickness (left superior parietal: r = 0.69, p = .0016; left precuneus: r = 0.56, p = .0160). Thus, the authors concluded that TPS as an add-on therapy can modify cortical thickness which leads to reduction of cortical atrophy in the stimulated regions.

Furthermore, Novak & Lohse-Busch (2022) conducted a longitudinal study involving 6 AD patients who underwent TPS treatment for three years. The authors stimulated the bilateral frontal cortex, bilateral lateral parietal cortex, extended precuneus cortex, and bilateral temporal cortex. The treatment protocol included an initial booster block of 6 sessions over two weeks, followed by a single re-treatment session per month after a 3-month follow-up period. After two years, a second booster treatment consisting of 6 sessions was administered. The results showed a 12.8% improvement in the CERAD score within the first three months, which was sustained for a

year through monthly re-treatments. However, it started declining significantly afterward, returning to baseline levels by the end of the second year, which was still better than the natural decline during the course of the disease. The CERAD scores remained better than the expected progression of the disease over another year, although the second booster treatment was less effective than the first. The authors suggested that more frequent booster treatments might maintain the improved CERAD scores beyond the first year of treatment.

In another study, Cont and colleagues (2022) recruited 11 AD patients (9 male) to evaluate the effects of TPS also targeting bilateral frontal cortex, bilateral lateral parietal cortex, extended precuneus cortex, and bilateral temporal cortex. Patients were assessed both at baseline and after TPS intervention over two weeks, and were further classified into three subgroups based on their MMSE scores: mild cognitive impairment (N = 4), moderate cognitive impairment (N = 5), and severe cognitive impairment (N = 2), with MMSE cut-off scores defined as follows: 30–27 for no impairment, 26–20 for mild impairment, 19–10 for moderate impairment, and <10 for severe impairment. The results showed significant improvements in both the ADAS total score and the ADAS-Cog score following TPS treatment. The ADAS total score decreased from a mean of 30.2 (SD = 11.55) to 25.8 (SD = 10.71), $t(8) = 2.87$, $p = 0.01$, reflecting a 15.76% improvement. The ADAS Cog score also showed an improvement, decreasing from a mean of 25.8 (SD = 0.77) to 23.3 (SD = 10.27), $t(8) = 2$, $p = 0.04$, corresponding to an 8.65% enhancement. However, no significant changes were observed in the MMSE scores (M = 17.64 [SD = 7.74] vs. 18 [SD = 7.12], $t(9) = -0.80$, $p = 0.22$) or the MoCA scores (M = 11.73 [SD = 6.2] vs. 12.09 [SD = 6.68], $t(9) = -0.13$, $p = 0.45$). Further analysis of subgroups revealed substantial improvement in the MMSE scores for both the severe and moderate groups, with a 20% mean improvement observed in the

severe group. Conversely, patients with mild symptoms exhibited a slight decline. The moderate impairment group demonstrated greater improvements across all tests compared to the mild impairment group. In the MoCA, the severe group showed a decline, while both the moderate and mild groups improved. Additionally, a one-tailed t-test indicated a significant reduction in self-reported depressive symptoms, which was measured by a subscale of the ADAS, from a mean of 0.7 (SD = 1.1) before stimulation to 0.2 (SD = 0.4) after stimulation, $t(8) = 1.859$, $p < 0.01$.

Moreover, Shinzato and colleagues (2024) conducted a study involving 10 AD patients with mild to moderate dementia to evaluate the effects of TPS treatment over time. A global brain stimulation approach was adopted, and targeted areas included frontotemporal, parietal, and occipital skull regions for 5 weeks consisting of 2 sessions per week with 6000 pulses per session. The authors used repeated measures ANOVA to assess changes from baseline in several outcome measures, including the ADAS-Cog, NPI, P-FAQ, and Zarit Caregiver Burden Interview scores at 30- and 90-days post-treatment, with time as a factor. They performed pairwise comparisons between baseline and two follow-up points (30 days and 90 days). The authors also stated that, due to the exploratory nature of the study, they did not perform multiple comparison corrections to minimize the risk of false negatives. While the change in ADAS-Cog scores did not reach statistical significance, there was a notable reduction in scores from baseline to 90 days post-treatment (mean difference of -3.6, 95% CI: -7.18 to 0.00, $p = 0.05$), suggesting a potential cognitive benefit of TPS in AD patients. The NPI scores demonstrated a significant improvement, with a mean reduction of 23.9 points at 30 days (95% CI: -39.19 to -8.61, $p = 0.0042$) and 18.9 points at 90 days (95% CI: -33.49 to -2.91, $p = 0.022$). These reductions reflect large effect sizes (Cohen's $dz = 1.43$ at 30 days and $dz = 0.94$ at 90 days) and are clinically meaningful, indicating

a significant decrease in the severity and frequency of neuropsychiatric symptoms in AD patients. However, changes in the P-FAQ scores were not statistically significant at any follow-up point compared to baseline ($M_{Baseline}$ = 21, M_{30days} =21, M_{90days} = 23). Similarly, the Zarit Caregiver Burden Interview scores did not show a statistically significant change over time ($M_{Baseline}$ = 27, M_{30days} =24, M_{90days} = 26).

In addition to the investigation of cognitive improvements in previous studies, Sprick and Köhne (2021) investigated the impact of TPS on cognitive and mood-related symptoms in 21 AD patients, focusing specifically on executive functions, and comorbid depressive symptoms. To evaluate the effectiveness of TPS, the authors stimulated the bilateral dorsolateral frontal cortex, bilateral parietal lobes, and bilateral temporal lobes (1000 pulses on each site per session). They conducted a pre- to post- comparison using the Stroop test for executive functions and the BDI for depressive symptoms. The results demonstrated a significant improvement in executive functions as measured by the Stroop test ($p < 0.05$). Notably, two patients exhibited a remarkable reduction in their test completion times, cutting their times by more than half within two weeks (from 575 seconds to 201 seconds, and from 602 seconds to 276 seconds, respectively). The mean completion time for the entire group decreased from 246 seconds to 166 seconds. Furthermore, the BDI scores showed a significant reduction, with an average decrease of 4.2 points after TPS treatment, indicating a notable improvement in mood. The statistical analysis confirmed a significant decrease in BDI scores (median change = -4.26) from baseline (Mdn = 28.33) to post-treatment (Mdn = 24.07), with a large effect size ($z = 7.43$, $p < .001$, $r = .64$).

Similarly, Matt and colleagues (2022b) explored the relationship between comorbid depressive symptoms and changes in functional connectivity following TPS treatment in a study involving 18 AD patients. The authors defined the targeted ROIs as follows: the bilateral frontal cortex extending to Broca's area, the bilateral lateral parietal cortex extending to Wernicke's area, and the extended precuneus cortex. The results demonstrated a significant reduction in depressive symptoms post-treatment, as indicated by a decrease in the average BDI-II score from 7.36 (SD = 5.09) at baseline to 5.00 (SD = 4.11) after stimulation, with the Wilcoxon test confirming this improvement (P = .037, two-tailed). Further, an ROI-to-ROI functional connectivity analysis using the CONN toolbox revealed that TPS treatment led to reduced functional connectivity (FC) between the left frontal orbital cortex (part of the ventromedial network) and the right anterior insula (part of the salience network). Notably, all patients initially showed positive FC between these regions at baseline. The analysis also identified a positive correlation between FC values and BDI-II scores (rho = .434, p = .021), indicating that higher FC values between these ROIs, which represent greater disruption of normal connectivity, were associated with more severe depressive symptoms. Therefore, reduced connectivity points out improvements in comorbid depressive symptoms in AD patients.

Additionally, Matt and colleagues (2020) conducted a single-blind RCT with 10 healthy participants to examine TPS effectiveness with different numbers of pulses. The study utilized neuronavigated TPS targeting the primary somatosensory representation of the right hand, and data were collected in one session using both a sham and TPS block. Each block included alternating runs of somatosensory-evoked potential (SEP) recordings (one baseline run and three runs approximately 20 seconds after TPS or sham stimulation) and TPS stimulation (three runs

with 10, 100, and 1000 pulses in a fixed order). A factorial design was used to analyze the effects of the Condition (Sham vs. Verum) and the Numbers of Pulses (10, 100, 1000). The analysis revealed significant effects for both condition and numbers of pulses, as well as a significant interaction between these factors. The main effect of the condition showed a notable reduction in the amplitude of the N140 SEP component (associated with conscious perception) for the verum condition compared to sham, consistent across different pulse numbers. Additionally, TPS was found to influence early components related to sensory processing in the primary and secondary somatosensory cortices, with increased N70 for 100 pulses and increased P27 and N70 for 1000 pulses. The authors concluded that the effects of TPS on EEG components linked to cortical somatosensory processing appear to strengthen with a higher number of pulses.

In another study, Matt and colleagues (2022a) conducted another single-blind RCT involving 20 right-handed healthy male participants to investigate the effects of TPS on the primary somatosensory representation of the right hand in the left postcentral gyrus. The authors utilized fMRI-based functional connectivity analysis to measure global efficiency (GE) within the left and right sensorimotor networks, which included regions such as the primary motor and somatosensory cortices, secondary somatosensory cortex, and higher-order integration areas. GE refers to the overall capacity for parallel information transfer and integrated processing between the nodes of a functional network. Additionally, DTI was used to estimate white matter microstructure changes by measuring fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity at a whole-brain level and within specific sensorimotor regions. Behavioral assessments for tactile spatial discrimination (2POD) and manual dexterity (CRT) were also conducted pre- and post-stimulation and correlation analysis was performed to explore the

relationship between TPS effects and behavioral outcomes. The results showed a significant increase in GE in the left sensorimotor network ($p = 0.040$), but not in the right network ($p = 0.210$). The precentral and postcentral gyri, superior parietal lobule, anterior supramarginal gyrus, and parietal operculum showed significant changes, which were the key hubs in the left sensorimotor network. Tract-based spatial statistics (TBSS) of DTI indices did not show significant effects on the white matter tract skeleton, but region of interest (ROI) analysis indicated significantly reduced axial diffusivity in the white matter tracts of the primary somatosensory ($p = 0.034$, FDR-corrected) and primary motor regions ($p = 0.038$, FDR-corrected) after verum TPS. Most participants showed decreased axial diffusivity in these regions following verum stimulation, while no consistent changes were observed after the sham. Voxel-based morphometry (VBM) analysis did not reveal significant grey matter volume changes. Factorial analysis of the CRT scores did not find significant effects related to the condition or session. Although performance in the 2POD task improved slightly post-stimulation in both verum and sham conditions, these differences were not statistically significant. Correlation analysis did not find significant relationships between neurophysiological measures (GE, axial diffusivity in the motor, and somatosensory ROIs) and behavioral outcomes, although a trend suggested a potential link between improved axonal integrity in the motor ROI and better tactile acuity ($\rho = 0.281$, $p = 0.056$).

In another study, Fong colleagues (2023) assessed the effectiveness of TPS on mild NCD in older adults. Nineteen participants completed a 12-week period of treatment-as-usual (TAU) followed by TPS intervention, with cognitive and psychological assessments conducted at baseline, after the TAU period, immediately after TPS intervention, and 12 weeks post-intervention. The study employed a global brain stimulation approach, delivering 6000 TPS pulses

per session distributed evenly across frontal, parietal, temporal, and occipital lobes. The primary outcome measure was the Hong Kong Chinese version of the MoCA, with secondary outcomes focusing on specific cognitive functions (e.g., attention, working memory, and executive function) assessed using various tests (Digit Span, Stroop, VFT, and TMT Parts A and B). Additionally, daily functioning was evaluated with the Hong Kong Chinese version of the IADL, depressive and apathy symptoms were assessed using the HDRS-17 and the AES-C, respectively, and serum BDNF levels and APOE genotype were measured. Repeated measures ANOVA demonstrated significant main effects of time on several measures, including the HK-MoCA ($F (3, 54) = 4.99$, $p = 0.004$), VFT (30-second interval, $F (3, 54) = 2.94$, $p = 0.041$), Stroop interference ($F (3, 54) = 3.46$, $p = 0.023$), and Chinese IADL ($F (3, 54) = 2.78$, $p = 0.050$). Post hoc analyses using Bonferroni adjustments indicated that HK-MoCA scores improved significantly immediately after the TPS intervention ($M = 21.16$, $SD = 3.98$) and at the 12-week follow-up ($M = 20.58$, $SD = 4.29$) compared to after the TAU period ($M = 18.74$, $SD = 3.87$) ($p < 0.05$). Participants also demonstrated faster performance in the Stroop interference task post-TPS ($M = 15.96$, $SD = 11.41$) compared to the TAU period ($M = 28.81$, $SD = 23.60$) ($p < 0.05$). In terms of psychological effects, while the only significant time effect was observed for daily functioning, there were trends indicating improvements in depressive symptoms and apathy following TPS intervention. Serum BDNF levels were lower after the intervention (Mean = 13.79 ng/mL, SD = 11.80) compared to before ($M = 21.00$ ng/mL, $SD = 14.30$), although this difference did not reach statistical significance ($t(16) = -1.57$, $p = .135$).

In the last study with older adults included in this review, Osou and colleagues (2023) evaluated the effectiveness of TPS on patients with PD. Twenty participants underwent ten

sessions of TPS over two weeks, targeting the primary sensorimotor area, supplementary motor area, and cingulate motor area. The primary outcome measure was the change in motor status as assessed by the UPDRS-III. The study found a significant improvement in UPDRS-III scores following TPS treatment, with mean scores decreasing from 16.70 (SD = 8.85) before treatment to 12.95 (SD = 8.55) after treatment ($p < 0.001$, Cohen's $d = 1.38$). Seven patients showed an improvement of at least five points, and none experienced a worsening of symptoms. The authors concluded that TPS led to a clear pattern of motor improvement without clinically relevant side effects, suggesting its potential as a beneficial adjunctive therapy for managing motor symptoms in PD.

Regarding the included study involving adults diagnosed with MDD, Cheung and colleagues (2023b) conducted a single-blind randomized controlled trial to assess the effectiveness of TPS. In their study, 30 participants were randomly assigned to either a TPS intervention group ($n = 15$) or a waitlist control (WC) group ($n = 15$). Both groups were evaluated at baseline (T1), immediately after 2 weeks of TPS treatment (T2), and at a 3-month follow-up (T3). TPS stimulation targeted the left dorsolateral prefrontal cortex (DLPFC), an area associated with hypoactivity in MDD patients (Grimm et al., 2008), delivering 300 pulses per session over two weeks (total of 6 sessions, 3 per week). The primary outcome, measured by HDRS-17, indicated a significant reduction in depression scores for the TPS group (from a mean of 25.73 to 13.20) compared to the WC group (from a mean of 21.60 to 19.80) at post-test ($p = 0.02$), with a large effect size of -0.93. Secondary outcomes, including measures of cognition, daily functioning, and anhedonia, also showed significant improvements over time. Notably, there were significant time effects on cognition ($p = 0.003$), TMT part A and B ($p < 0.001$ for TMT A, $p = 0.07$ for TMT B),

IADL ($p < 0.001$), SHAPS ($p < 0.001$), and working memory ($p = 0.003$ for forward digit span, $p < 0.001$ for backward digit span). Furthermore, the study reported sustained reductions in depression severity at the 3-month follow-up, with a large effect size for depression ($d = 1.35$) and very large effect sizes for global cognition, TMT B, and backward digit span ($d = 1.2$, 1.1, and 1.09, respectively). Medium to large effect sizes were observed for other secondary outcomes. With the exception of the forward digit span ($p = 0.2$), all primary and secondary outcomes were statistically significant ($p < 0.001$).

Another study included in this review was conducted by Cheung and colleagues (2023a) with ASD patients. In this double-blind RCT, the authors evaluated the efficacy and tolerability of a 2-week TPS treatment in young adolescents diagnosed with ASD (total of 6 sessions, 3 per week). A total of 32 participants were randomly assigned to either a TPS intervention group ($n = 16$) or a sham stimulation group ($n = 16$). The right temporoparietal junction (rTPJ), a region associated with social cognition deficits in individuals with ASD, was targeted, with 800 pulses delivered per session. Outcomes were measured at four time points: baseline (T1), immediately after the 2-week intervention (T2), 1-month follow-up (T3), and 3-month follow-up (T4). The primary outcome was the CARS, while secondary outcomes included the AQ, the ASAS, the SRS, and various cognitive and behavioral tests such as TMT, VFT, Stroop test, Digit Span Test (forward and backward), and CGI. The study found a significant reduction in the severity of ASD symptoms immediately after the TPS intervention, as measured by the CARS score, which decreased from a mean of 30.81 ($SD = 5.91$) to 23.56 ($SD = 6.5$) ($P < 0.001$). Improvements in social and emotional domains, such as relating with people, emotional response, adaptation to change, and verbal communication, remained statistically significant at the 3-month follow-up (all

$P < 0.05$). Some effects, such as those on object use and listening response, became non-significant by the 1- and 3-month follow-ups ($P>0.05$). Interestingly, certain sensory and non-verbal communication responses showed delayed improvement, becoming statistically significant only at the 1- and 3-month follow-ups (P-values changed from 0.069 to 0.034). Overall, there was a 24% reduction in the average total CARS score from baseline to post-intervention, with sustained effects observed at both the 1-month [mean = 23.44 (SD = 7.2)] and 3-month [mean = 23.56 (SD = 6.5)] follow-ups ($P < 0.05$). The TPS group demonstrated significant improvements in CARS and CGI scores immediately after the intervention, with sustained effects up to 3 months post-intervention compared to the sham group (all $P < 0.05$). The effect sizes for CARS ($d = 0.83–0.95$) and CGI improvement ($d = 4.12–4.37$) were large to medium immediately after treatment and at 1-month post-stimulation, but these effects became small by the 3-month follow-up.

In the final study included in this review, Cheung and colleagues (2024) investigated the effectiveness of TPS intervention on ADHD. In this double-blind RCT, the authors investigated the efficacy and safety of TPS in young adolescents (aged 12–17 years) with ADHD in Hong Kong. The study assessed TPS's impact on core ADHD symptoms, including inattention, hyperactivity, impulsivity, oppositional defiance, and executive functions, as well as brain functional connectivity changes via fMRI after 2 weeks of TPS treatment. Thirty-two participants were randomly assigned to either a verum TPS group ($n = 17$) or a sham TPS group ($n = 15$). The treatment targeted the left dorsolateral prefrontal cortex (DLPFC) in accordance with previous literature suggesting under-activation of the prefrontal cortex and deficits in Working Memory associated with ADHD (Sotnikova et al., 2017). 800 pulses per session were delivered across six sessions over two weeks (3 sessions per week). Participants were evaluated at baseline,

immediately after the 2-week intervention, and at 1-month and 3-month follow-ups. The primary outcome was measured using the SNAP-IV for inattention, hyperactivity/impulsivity, and oppositional defiance. Secondary outcomes included the CGI-S and CGI-I scales, the Stroop test for executive functions, and the ADHD RS-IV. A linear mixed model was used to analyze the group (TPS vs. sham) and time (baseline to follow-ups) effects on the outcome scores. Results showed no significant differences between the groups at baseline ($p > 0.05$). However, after TPS intervention, significant interaction effects were observed in the SNAP-IV, ADHD-RS-IV, CGI-S, CGI-I, CGI total scores, and response times on the Stroop test in the word reading, color naming, and named color-word conditions (all $p < 0.05$). Post hoc comparisons revealed that the TPS group had significantly lower mean SNAP-IV scores at post-test and at 1-month and 3-month follow-ups compared to the sham group (all $p < 0.001$), with large effect sizes (Cohen's $d = 2.32$, 2.45, and 2.40, respectively). Additionally, for secondary outcomes, the TPS group showed significant improvements with large effect sizes in ADHD-RS-IV ($d = 1.04$), CGI-I ($d = 1.04–5.63$), and CGI total scores ($d = 1.13–2.69$). These results suggest that TPS may be an effective intervention for reducing ADHD symptoms and improving overall functioning in adolescents with ADHD. In terms of neuroimaging results, the authors stated that the results will be combined with the neuroimaging results of their ASD study and published in another paper in the future.

3.4.2. Safety Profile of TPS

In line with the findings of the individual studies in the previous section, safety profile results from the included TPS studies in this review will be presented in the same order in this section. These results will cover adverse effects, such as headache, mood deterioration, perceived pain and pressure, and any intracranial pathology like hemorrhage, and brain lesions.

Firstly, Beistenier and colleagues (2020) reported that patient evaluations conducted at both centers over a three-month follow-up period (involving clinical examinations, patient reports, and MRI scans) showed no significant side effects. At Center 1, a detailed assessment found that 4% of patients experienced headaches (some with a pre-existing history), 3% reported mood deterioration, and 93% reported no side effects. Pain or pressure experienced during treatment, assessed on a visual analog scale (VAS 0–10), indicated that 92% of patients reported no pain (VAS 0), 7% reported mild pain (VAS 1–5), and 1% reported moderate pain (VAS 6–8). For pressure, 83% reported no sensation (VAS 0), 15% reported mild pressure (VAS 1–5), and 2% reported moderate pressure (VAS 6–8). Furthermore, no signs of hemorrhages, edema, or any other new intracranial pathology were observed during MRI evaluations, including T2* and FLASH images.

Unfortunately, five of the included studies in this review did not report the adverse effects following TPS intervention (Dörl et al., 2022; Matt et al., 2020; Matt et al., 2022b; Novak et al., 2022; Popescu et al., 2021). However, missing information about the adverse effects in these studies can be neglected, as they were conducted based on the recruitment of participants from the study by Beisteiner and colleagues (2020). On the other hand, adverse effects and safety profile in the study by Shinzato and colleagues (2024) were not reported at all.

Secondly, Cont and colleagues (2022) utilized the NRS to assess the adverse effects and safety profile of TPS. The findings showed that 3 out of 11 patients (27%) experienced side effects in 3 out of 75 sessions (4%). These side effects included jaw pain (NRS 4/10), nausea (NRS 7/10), and drowsiness (NRS 10/10). Medical evaluations, including blood count, blood sugar, and blood

pressure, could not determine the cause of one patient's drowsiness, and external factors could not be ruled out. However, none of the side effects persisted for more than a day, and no permanent side effects were observed.

Furthermore, Sprick and Köhne (2021) reported that only two out of twenty-one patients reported temporary side effects after TPS treatment: one with temporary headaches in the forehead area, and other transient general fatigue after the stimulation

.

In the next study with AD patients, Matt and colleagues (2022a) stated that participants frequently reported sensations on the scalp, with tactile experiences like "knocking" being noted under both conditions. Pressure and pain at the scalp were mentioned more often in the verum condition, but the average intensity of these sensations remained low, typically between 2 and 3 on a 10-point scale. Other than a single occurrence of left thigh twitching during a verum TPS session, no additional peripheral sensations were recorded.

Conversely, Fong and colleagues (2023) only stated that no major adverse effects were observed during TPS intervention, however, the authors did not provide further information about if the minor adverse effects were observed.

On the contrary, Osou and colleagues (2023) provided the details of safety evaluations and stated that, during the TPS intervention period, no serious adverse effects were observed. A total of 13 patients (65%) experienced at least one mild adverse event over the 10 days of TPS treatment. Fatigue, headache, and dizziness, reported by 10 patients (50%), 6 patients (30%), and 6 patients

(30%), respectively, were the most frequently reported adverse effects. However, these disappeared within a day after treatment. Visual Analogue Scale (VAS) assessments (on a scale of 0–10) for pressure experienced during treatment indicated that 91.5% of sessions were rated as VAS 0, 3.5% were rated between 1–3, 4% between 4–6, and 1% between 7–8.

In their study with MDD patients, Cheung and colleagues (2023b) reported that they prepared a checklist to monitor the possible adverse effects of TPS treatment. Authors stated that 4% of their patients experienced headaches but none of them needed pain analgesics. Moreover, one subject experienced nausea and vomiting after the first session, but these symptoms were resolved in 2 hours.

In the next study by Cheung and colleagues (2023a) with ASD patients, an adverse event checklist was used to monitor adverse effects during and after TPS intervention. Five participants in the verum TPS group experienced transient headaches during stimulation, and these were rated between 3 to 5 on a 10-point pain scale and resolved immediately after the TPS sessions without requiring any analgesics. In contrast, the sham TPS group reported no adverse events, and no parents noted any somatic discomfort in participants once they returned home throughout the intervention period.

In the last study included in this review, Cheung and colleagues (2024) reported that 3 out of 17 participants in the verum group experienced mild headaches, and the mean pain score was 4/10. However, the pain duration did not exceed 3 minutes. Moreover, no adverse effects were

reported in the sham stimulation group, and parents did not declare any side effects after treatment sessions.

In conclusion, TPS seems to be a well-tolerated and safe intervention across different patient groups, and other non-clinical conditions. Most reported adverse events were mild and transient, such as headaches, dizziness, or sensations at the scalp, with minimal pain intensity and no need for medical intervention. Serious side effects or significant clinical complications were not observed in any of the studies. Furthermore, both clinical evaluations and neuroimaging data (MRI scans) consistently showed no evidence of intracranial pathology, such as hemorrhages or edema, following TPS treatment. The findings indicate that TPS is a safe and feasible treatment option, with a favorable safety profile that supports its use in clinical settings.

3.4.3. Limitations and Challenges of the Included Studies

As most of the included studies are the first pilot trials with their target population regardless of their study design, they suffer from some limitations.

To begin with, several studies included in this review shared some common limitations. A frequently noted constraint was the lack of a sham control group, which affects the ability to clearly distinguish the effects of TPS from placebo effects and causes the internal validity to be low in these studies (Beisteiner et al., 2020; Cont et al., 2022; Dörl et al., 2022; Matt et al., 2022b; Novak et al., 2022; Osou et al., 2023; Popescu et al., 2021; Shinzato et al., 2024; Sprick & Köhne, 2021). Another recurrent issue was the small sample size across studies, limiting the generalizability and statistical power of their findings (Cheung et al., 2024; Cont et al., 2022; Dörl et al., 2022; Fong

et al., 2023; Matt et al., 2022a, 2022b; Novak et al., 2022; Osou et al., 2023; Shinzato et al., 2024; Sprick & Köhne, 2021). Additionally, several studies called for longer-term investigations to determine the sustained effects of TPS (Dörl et al., 2022; Matt et al., 2022b; Popescu et al., 2021).

Additionally, several limitations were also reported across individual studies included in this review. Firstly, Beisteiner and colleagues (2020) suggested that future studies should consider comparing patient subgroups in terms of disease stage, antidementia therapy, comorbidities, and cognitive status for a more nuanced evaluation of the effectiveness of TPS. Additionally, the authors also recommended some procedural optimizations for developing more standardized TPS parameters related to local skull thickness and focal energy within the brain. Secondly, Dörl and colleagues (2022) pointed out the absence of long-term fMRI data beyond 6 weeks and the reliance on a single follow-up time point for fMRI measurements. Similarly, Popescu and colleagues (2021) also suggested further investigations to explore morphological changes over longer durations for better generalization of the observed neuropsychological effects that persisted for three months. In a similar fashion, Fong and colleagues (2023) also suggested that a two-week intervention period could be considered insufficient, and therefore, longer intervention periods should be taken into account to better explain the long-lasting TPS effects. Moreover, Novak and Lohse-Busch (2022) proposed an evaluation of more frequent re-treatment and booster sessions for acquiring more sustained TPS treatment effects. The major limitation of the study by Cont and colleagues (2022) was that, instead of acquiring real-time data, they conducted a retrospective analysis which suffered from missing data, because it relied on clinical databases. Furthermore, Matt and colleagues (2022a) reported that their study focused on only the long-term therapeutic effects of TPS, and future studies should also consider the immediate effects after the intervention.

Additionally, in the study by Matt and colleagues (2020), a fixed order of the number of TPS pulses was utilized, which may cause a subject-expectancy effect. Therefore, future studies should adopt better blinding strategies. Besides, a larger sample size with a spontaneous intervention and sham-controlled group is necessary, as all the patients in this study took part in both groups at different time points. Next, Osou and colleagues (2023) suggest that further studies should recruit a more homogeneous group of patients as their participants were included regardless of comorbidities as long as they complied with PD inclusion criteria. Likewise, Cheung and colleagues (2023a) also emphasized on the fact that future studies should look for multicentral collaborations to include more diverse age groups of ASD patients, as there is a lack of consensus in the literature on stimulation targets for various ages. In their other study with MDD patients, Cheung and colleagues (2023b) made a similar recommendation by stating that future studies should consider including individuals with severe depression to investigate the effectiveness of TPS across different MDD severities. Additionally, the authors also addressed the limitation of their study relying on self-report data and encouraged future investigations for the utilization of better measurements to increase the objectivity of the results. By the same token, in the last study included in this review with ADHD patients, Cheung and colleagues (2024) also suggested that a study with multicentral collaborations should be carried out to increase generalizability, as their study was conducted on a single site. Additionally, participants with severe symptoms attending special schools were excluded, and medication adherence was inconsistent. Therefore, the authors advised the inclusion of participants that represent all levels of severity and better monitoring of medication adherence.

4. Discussion

Over the last decade, interest in the use of ultrasound-based NIBS methods has increased greatly, as it holds potential for new therapeutic strategies. Similar to the emergence of variations on other NIBS techniques such as repetitive TMS or accelerated TMS, different types of ultrasound-based methods are also being developed, such as fTUS and most recently TPS. To our knowledge, this is the first systematic review to evaluate the findings of all TPS studies with human participants regardless of their (healthy or pathological) condition. In light of this, this review included 15 studies to provide a comprehensive synthesis of current evidence on the neuromodulatory effects of neuronavigated TPS across diverse populations, including patients with neurological disorders such as AD, PD, and mild NCD, developmental disorders like ASD and ADHD, and MDD. The review also considers studies involving healthy participants, thus offering a broad perspective on the potential of TPS as both a therapeutic intervention and a tool for neuroenhancement. By examining the effectiveness of TPS across three primary outcome domains, neuropsychological outcomes, neuroimaging outcomes, and improvements in behavioral symptoms, social functioning, and daily life, this review aims to elucidate the clinical applicability and therapeutic potential of TPS. Furthermore, by identifying limitations in the existing literature, it highlights areas requiring further investigation and suggests directions for future research to optimize the use of TPS in clinical practice. The findings of this review have the potential to inform treatment strategies, refine clinical guidelines, and advance our understanding of TPS as an innovative neuromodulation modality.

4.1. Summary of Findings and Comparison with Existing Literature

As mentioned in the previous sections of this review, the findings of the included studies were investigated across three domains, as follows: neuropsychological outcomes, neuroimaging outcomes, and improvements in behavioral symptoms, social functioning, and daily life. In this section of the review, this strategy will be also organized according to the target population for a clearer summary of the effectiveness of TPS.

To begin with the studies with patient groups, this review included eight studies of TPS intervention on patients with AD. In these studies, TPS stimulation targeted the bilateral frontal cortex (dorsolateral prefrontal cortex and inferior frontal cortex extending to Broca's area), bilateral lateral parietal cortex (extending to Wernicke's area), or extended precuneus cortex. These areas were chosen to focus on the dysfunctional dlPFC activity associated with impairment of working memory (Kumar et al., 2017), and regions of the memory network including default mode and language networks (Beisteiner et al., 2020). In addition to the stabilization of symptoms, TPS intervention targeting these areas also led to cognitive improvements and neuropsychological benefits, which were sustained for up to three months in the majority of the included studies. Significant improvements in CERAD neuropsychology test (Beisteiner et al., 2020; Dörl et al., 2022; Novak et al., 2022; Popescu et al., 2021), ADAS-cog (Cont et al., 2022; Shinzato et al., 2024), Stroop test (Sprick & Köhne, 2022), MMSE (Cont et al., 2022), MoCA (Cont et al., 2022) scores were observed. In the studies by Beisteiner et al. (2020) and Dörl et al. (2022), further analysis also enabled the authors to separately monitor changes in memory, verbal processing, and visuospatial processing. While improvements in memory and verbal processing were found, the visuospatial processing showed a trend of declining. These results are in line with the existing

literature. For instance, Ahmed and colleagues (2012) stated that MMSE, IADL, and GDS results were significantly improved in the high-frequency rTMS (20 Hz, excitatory TMS) group compared to low-frequency (1 Hz, inhibitory TMS) and sham group of AD patients, and the authors concluded that these improvements were associated with the stimulation of the bilateral dlPFC. Additionally, in terms of the utilization of low-intensity TUS, Shimokawa and colleagues (2022) analyzed data from 19 patients with AD, and used the Japanese version of ADAS-Cog as the primary outcome measure. The results showed that global cortical stimulation through temporal bones led to stabilization of the ADAS-Cog scores over 72 weeks after intervention while it continued to gradually decline in the sham control group. These findings were further supported by neuroimaging results. In 4 of the included studies with AD patients, fMRI was utilized to investigate the changes in network activity (Beisteiner et al., 2020; Dörl et al., 2022), rsFC (Beisteiner et al., 2020; Matt et al., 2022b), task-related connectivity (Beisteiner et al., 2020), and cortical thickness (Popescu et al., 2021). Firstly, Beisteiner and colleagues (2020) observed increased functional activation in the hippocampal areas in the fMRI data during a face-name encoding task with a subgroup of participants, post-TPS compared to baseline. Moreover, following TPS, increased GE of the memory network was also found in bilateral (para-) hippocampal and parietal areas, and precuneus. The authors concluded that the upregulation in the memory network is associated with increased cognitive performance, as significant correlations were found between improved CERAD scores and functional connectivity. Comorbid depressive symptoms in AD patients were also taken into account and assessed before and after TPS intervention. Significant improvements, from baseline to 3-month post-stimulation, in the BDI scores (Beisteiner et al., 2020; Matt et al., 2022b; Sprick & Köhne, 2022), and the GDS scores (Beisteiner et al., 2020) were observed. Matt and colleagues (2022b) also investigated ROI-to-ROI

functional connectivity to evaluate the antidepressive effects of TPS. Their results showed that the TPS treatment resulted in improved abnormal rsFC between the left frontal cortex and the right anterior insula, and this improvement was positively correlated with ameliorated depressive symptoms in AD patients. In a similar fashion, a single-blind RCT included in this review was also conducted to evaluate the benefits of TPS targeting the left dlPFC in adults with MDD (Cheung et al., 2023b). The authors utilized HDRS-17, SHAPS, IADL, and MoCA to measure changes in depressive symptoms, apathy, motivation in daily activities, and global cognition, respectively. Participants in the verum group showed significant improvements in depression scores, anhedonia, IADL, working memory, and executive functions compared to the sham condition, and these improvements remained significant up to the 3-months FU. Several studies in the literature also support these results following TPS intervention. Correspondingly, a TMS study adopted 10 Hz rTMS over the left lateral parietal region, as this region showed high functional connectivity with the left hippocampal seed in their rsFC data (Wei et al., 2022). The authors found that, in default mode network (DMN), the verum group of AD patients exhibited higher magnitudes of dynamic functional connectivity (dFC), which refers to changes in FC over a short period of time, and the increase in dFC was positively correlated with improvements in MMSE scores in the rTMS compared to sham condition. Moreover, low-intensity fTUS targeting the left dlPFC was utilized to investigate alterations in functional connectivity in MDD patients (Oh et al., 2024). The authors stated that depressive symptoms were significantly improved, and increased rsFC was found between subgenual anterior cingulate cortex (sgACC) and bilateral medial prefrontal cortex in the verum compared to the sham group. In terms of investigating anatomical changes in AD patients after TPS, Popescu and colleagues (2021) adopted a surface-based morphometry approach to examine the changes in cortical atrophy, and its correlation with

improved CERAD scores. Their results revealed that TPS resulted in significant pre-to-post improvements in CERAD scores, and these improvements were significantly correlated with changes in the cortical thickness of AD-related brain regions. These regions included the left superior parietal lobule and left precuneus, which are AD-critical DMN structures. In conclusion, the authors claimed that TPS as an add-on therapy can reduce cortical atrophy by modulating cortical thickness in the targeted areas. Similarly, Boes and colleagues (2018) conducted a study to assess the effectiveness of high-frequency rTMS (10 Hz) targeting the left dlPFC on inducing changes in cortical thickness in 45 patients with treatment-resistant MDD. Their results showed that depressive symptoms were significantly improved in all participants and 19 of them were grouped as "responders" according to at least a 50% reduction in their BDI scores. Further analysis revealed a significant correlation between improvements in depressive symptoms and increased cortical thickness in the left rostral anterior cingulate cortex (rACC). Moreover, increased cortical thickness in rACC was significantly different between responders and non-responders. A trend in increased thickness was observed in responders compared to a significant decrease in non-responders. In addition to cognitive impairments and comorbid depressive symptoms, AD also causes disturbances in the social and daily life of both patients and their caregivers. To evaluate dysfunctions in abilities required in social and daily life, the NPI, P-FAQ, and Zarit caregiver burden interview were used in the study by Shinzato and colleagues (2024). Although the results showed significant improvements in the NPI scores following the TPS treatment that sustained up to 3-months FU, the P-FAQ and Zarit caregiver burden scores did not reveal significant improvements. However, these results are not consistent with the existing literature using other neurostimulation techniques. For example, studies on the effectiveness of rTMS on AD, results revealed significant improvements in AD patients' daily living abilities measured by the IADL

(Cotelli et al., 2011; Padala et al., 2020; Wei et al., 2022). To sum up, in the findings of the included studies with AD patients, neuronavigated TPS was shown to be an effective treatment method by stabilizing and improving cognitive functions, and comorbid depressive symptoms in addition to increased rsFC, task-related connectivity, and cortical thickness. These results are consistent with the existing literature on studies with different NIBS techniques such as TMS and TUS.

Moreover, Osou and colleagues (2023) investigated the effectiveness of neuronavigated TPS in PD patients. The authors focused on the stimulation of the motor network including the primary sensorimotor area, supplementary motor area, and cingulate motor area, and measured the changes in motor symptoms with UPDRS-III. Their results showed that the patients demonstrated significant improvements in motor symptoms after TPS intervention. These results were also supported by a systematic review investigating the effects of rTMS on motor symptoms in PD (Chou et al., 2015). The authors stated that high-frequency (excitatory) rTMS over motor areas (M1 and SMA) appears to be the most effective in ameliorating motor symptoms in PD patients, as hypoactivity in these areas is highly associated with PD.

Additionally, Fong and colleagues (2023) assessed the effectiveness of TPS on mild NCD patients with a global brain stimulation approach. The authors utilized several outcome measures to evaluate improvements in different aspects such as cognitive functions with MoCA, digit span test, Stroop test, VFT, and TMT, skills of daily living activities with IADL, and comorbid depressive symptoms with HDRS-17 and AES-C. Moreover, blood samples were also collected before and after TPS treatment to monitor changes in BDNF serum concentration. The results showed that global cognition was significantly improved and maintained for at least three months

after TPS intervention. Moreover, the Stroop test also showed significant improvements in executive functions. On the contrary, BDNF serum concentration did not show significant changes, and no significant correlations were found between BDNF and cognitive improvements. The cognitive improvements found in this study are in line with the literature. For instance, Drumond Marra and colleagues (2015) showed that high-frequency (excitatory) rTMS (10 Hz) over the left dlPFC led to significant improvements in performance on the Rivermead Behavioral Memory Test, and TMT, with significant differences between the verum and sham condition. Additionally, Nicodemus and colleagues (2019) also showed the effectiveness of fTUS on patients with AD. Their results showed significant improvements in MoCA and the Repeatable Battery for Assessment of Neuropsychological Status scores after fTUS stimulation targeting the bilateral hippocampus. As opposed to BDNF results by Fong and colleagues (2023), increased BDNF expression following fTUS and microbubbles in the mouse model of AD was found in several studies (Burgess et al., 2011; Scarcelli et al., 2014; Tufail et al., 2010).

Two of the included studies in this review were conducted by Cheung and colleagues (2023a; 2024) to assess the effectiveness of TPS on developmental disorders such as ASD and ADHD. Firstly, a double-blind RCT was conducted to evaluate the treatment effects of TPS on adolescents with ASD (Cheung et al., 2023a). The authors targeted the rTPJ of 32 participants and monitored the changes by using the CARS, AQ, digit span test, ASAS, SRS, TMT, VFT, Stoop test, and CGI. Regardless of ASD severity, participants showed a significant reduction in CARS scores in verum compared to sham condition, which was sustained up to 3-months post-stimulation. Additionally, core ASD symptoms were successfully reduced by 24%, and the CGI results supported this by revealing a 53.7% decrease in core ASD symptoms in the TPS group

compared to the sham control group. In terms of cognitive improvements, results also showed significant improvements in VFT and digit span tests, as well as in social cognition and communication skills by highlighting ameliorations in verbal fluency and working memory within the TPS intervention group. On the other hand, in their second study, Cheung and colleagues (2024) utilized neuronavigated TPS targeting the left dlPFC to investigate the efficacy and safety of TPS in young adolescents with ADHD. The outcome measures consisted of the SNAP-IV, CGI, Stroop test, and ADHD RS-IV. The results revealed that the TPS group demonstrated a significant decrease in SNAP-IV scores, indicating improved inattention and hyperactivity/impulsivity, compared to the control group. Additionally, significant improvements were also found in ADHD RS-IV, CGI-I and CGI total scores in the TPS group. Although TMS is based on different mechanisms, there are some studies in the literature assessing its effectiveness on ASD and ADHD symptoms. For example, Casanova and colleagues (2012) utilized low-intensity rTMS (1 Hz) over bilateral dlPFC of adolescents with ASD to assess changes in abnormal cortical inhibition measured by Kanizsa Illusory Figure Test. As augmented and prolonged event-related potentials (ERP) to irrelevant stimuli during visual perception and attention in ADHD were observed in their previous study, the authors also utilized EEG to monitor the changes in ERPs in visual processing (N200, P300). Their results showed significant improvements in both ERP components. After rTMS intervention, the amplitude of N200 to task stimuli was significantly more negative than to task-irrelevant stimuli, and its latency decreased significantly to task relevant target. Equivalently, P300 to target stimuli also resulted in increased amplitude and decreased latency. These findings are associated with a significant decrease in response errors and enhanced selective attention by improving visual discrimination process and better processing of irrelevant stimuli. Similarly, Sokhadze and colleagues (2012) utilized 1 Hz rTMS over the left and right dlPFC (6 weeks of

stimulation on each site, one session per week) to assess reaction time, error rate, and changes in ERP components (ERN - error-related negativity, Pe – error-related positivity). Results revealed improved performance in visual attention task manifested by reduced error rate, decreased ERN latency, and augmented ERN amplitude. In the context of ADHD, Weaver and colleagues (2012) used 10 Hz rTMS targeting the right PFC of young adults with ADHD. Although their results did not show significant improvements in neuropsychological measures, the authors stated that the CGI and ADHD-IV scales showed overall improvements across the study in rTMS compared to the control group.

Lastly, in two of the included studies, Matt and colleagues (2020; 2022a) examined the effectiveness of neuronavigated TPS on healthy participants. Firstly, the authors conducted an EEG study with 10 healthy participants to assess whether the number of TPS pulses (10/100/1000) yielded different outcomes (Matt et al., 2020). In this single-blind RCT, TPS targeted the left postcentral gyrus to observe its effects on SEPs. The results showed significant changes in the amplitudes of several SEPs as follows: reduction in N140 (related to conscious perception) across different numbers of pulses, increased N70 for 100 pulses, and increased P27 and N70 for 1000 pulses. The increase in these SEP components indicates better cortical somatosensory processing with a higher number of pulses. Several studies in the literature adopting different neuromodulation techniques also found similar results. To illustrate, increased N20 and P27 amplitudes after low-intensity rTMS (1 Hz) over S1 (Meehan et al., 2011), elicited SEP following fTUS over S1 without causing stimulation-related artifacts (Kim et al., 2023). In their other study with 20 healthy participants, Matt and colleagues (2022a) investigated the effects of TPS over the left postcentral gyrus on task performance measured with the 2POD and CRT tasks. The authors

also adopted fMRI to observe changes in rsFC, and DTI to assess alterations of the white matter microstructure. Their results showed that GE of the stimulated left sensorimotor network was significantly increased although there were no significant differences in DTI indices pre-to-post TPS intervention, and performance on the 2POD and CRT was slightly improved. Additionally, correlation analysis showed a trend for an association between improved task performance and an increase in axonal diffusivity. Similarly, Nowak and colleagues (2008) revealed that low-intensity rTMS (M1) to the contra-lesional M1 in stroke patients improved manual dexterity and grasp movements. Moreover, Dafotakis and colleagues (2008) also achieved similar results with healthy participants. By applying 1 Hz rTMS over the left M1, participants' performance on finger and hand tapping, and grasping was improved in the ipsilateral hand. The authors interpreted these findings by suggesting that transcallosal inhibition is declined by 1 Hz rTMS induced inhibition, resulted in improved performance in the ipsilateral hand.

To sum up, although TPS is a novel technique, it has been shown that it can be a safe and effective add-on therapy tool across a variety of neurological and psychiatric conditions, as well as a method for neuroenhancement for healthy populations.

4.2. Implications for Clinical Practice

The results of this systematic review highlight the potential for neuronavigated TPS as a promising neuromodulatory intervention for various neurological and psychiatric conditions. For clinicians working with AD patients, TPS represents a novel, non-invasive treatment option that has demonstrated significant improvements in cognitive functions, such as working memory, verbal processing, and overall neuropsychological performance, as measured by tests like CERAD

and ADAS-cog. The sustained effects of TPS, observed up to three months post-intervention, could offer, if confirmed by further studies, a practical therapeutic tool that could complement existing treatments and potentially delay symptom progression. Moreover, improvements in comorbid depressive symptoms, as evidenced by better BDI and GDS scores, suggest TPS could address both cognitive and mood disturbances in AD, contributing to a more holistic patient care approach.

Beyond AD, neuronavigated TPS also shows clinical promise in treating MDD, PD, and NCD. In MDD, TPS targeting the dorsolateral prefrontal cortex (dlPFC) has been linked with significant improvements in depressive symptoms, anhedonia, and executive functioning, which were sustained for up to three months. This could inform clinical strategies aimed at treating MDD, especially in cases where patients are resistant to conventional therapies. In PD, TPS targeting motor-related areas, such as the primary sensorimotor area and supplementary motor area demonstrated significant improvements in motor symptoms, reinforcing its potential as a complementary therapy to traditional pharmacological treatments. Additionally, TPS has shown neurocognitive benefits in patients with mild NCD, improving executive functions, global cognition, and daily living skills, which could enhance patients' quality of life.

Lastly, the review underscores neuronavigated TPS's potential role in neuroenhancement for healthy individuals. Studies on healthy participants showed that TPS can modulate sensory and motor processing, as well as cognitive task performance, making it a potential tool for cognitive enhancement or rehabilitation in non-clinical populations. While more research is needed, these

findings suggest that TPS could be integrated into clinical practice as a versatile neuromodulation tool, applicable across a wide spectrum of conditions and patient needs.

In conclusion, the growing body of evidence supporting TPS's effectiveness and safety opens new avenues for its clinical application, and it could serve as an add-on or standalone treatment in neurological, psychiatric, and cognitive domains.

4.3. Strengths and Limitations of the Review

This review provides a comprehensive analysis of the current evidence regarding the effectiveness of neuronavigated TPS on various neurological and psychiatric conditions. One key strength of the review is the inclusion of studies across a diverse range of populations, from AD and PD to developmental disorders such as ASD and ADHD, as well as studies involving healthy participants. This broad scope enhances the general understanding of TPS as a therapeutic and neuroenhancement tool. Furthermore, the review highlights the potential of TPS to improve cognitive functions, depressive symptoms, motor abilities, and social functioning. The integration of neuroimaging data (fMRI, DTI, EEG) alongside behavioral and cognitive outcome measures provides a valuable multidimensional perspective on the potential mechanisms of TPS, including changes in functional connectivity and cortical thickness. Additionally, this review finds consistent results in cognitive and neuropsychological improvements across multiple studies, reinforcing the evidence for TPS’s efficacy. The inclusion of several longitudinal follow-up studies also adds value by showing that TPS effects can be sustained for up to three months post-intervention. The cross-comparison with other non-invasive brain stimulation techniques (e.g., TMS, TUS)

strengthens the position of TPS, as a novel technique, within the broader context of brain stimulation research.

However, several limitations affect the robustness of the findings of this review. First, a critical limitation is the absence of a meta-analysis due to the heterogeneity in study designs, outcome measures, and patient populations across the included studies. Without quantitative synthesis, it is difficult to provide a precise estimate of the overall effect size of TPS interventions, and the conclusions remain more qualitative in nature. Future systematic reviews should aim to include meta-analyses when more homogeneous data will become available to allow for a more rigorous and quantitative assessment of the efficacy of neuronavigated TPS.

4.4. Limitations of Reviewed Studies

Firstly, a notable issue across many of the included studies (10 out of 15) is the lack of a sham control group, which limits the ability to account for placebo effects and reduces the internal validity of the results. Without proper control conditions, distinguishing TPS-specific effects from non-specific improvements becomes challenging. In addition, the small sample sizes of most studies reduce the statistical power and generalizability of the results. Larger, ideally multicenter studies are needed to validate and extend the current findings and increase the external validity across different populations.

Another limitation concerns the short follow-up periods. While several studies demonstrated cognitive and neuropsychological improvements over 3 months, longer-term data are necessary to assess the sustainability of TPS effects, especially in progressive

neurodegenerative diseases like AD, NCD, and PD. Many studies also lacked rigorous blinding procedures, which can introduce biases. For example, two of the included studies in this review adopted a single-blind design, and only participants were blinded about their grouping. This strategy might cause to the experimenter bias. Additionally, a fixed order of the number of pulses was chosen in one study included in this review. This lack of randomization may also cause the demand characteristics.

Lastly, while neuroimaging data, fMRI and DTI, offered valuable insights into changes in FC, functional activity, and cortical thickness, several studies were limited by the absence of long-term neuroimaging data beyond initial follow-up periods, preventing a thorough understanding of the stability of anatomical changes associated with TPS.

In summary, while this review highlights promising evidence supporting the potential of TPS as an effective intervention across multiple neurological and psychiatric conditions, future studies should aim to address these limitations through the inclusion of sham controls, larger sample sizes, long-term follow-ups, and consistent outcome measures.

4.5. Future Researcher Directions

Given the promising results of TPS across various neurological and psychiatric disorders, future research should prioritize targeting deeper brain regions associated with specific disease mechanisms. For instance, the dentate gyrus, a critical region for adult hippocampal neurogenesis (Benarroch, 2013), could be targeted in patients with neurodegenerative diseases, such as those with AD. This would build on the potential of TPS to stimulate neurogenesis, as well as promote

memory formation, cognitive restoration, and information processing. These assumptions were also supported by animal experiments utilizing fTUS. Scarcelli and colleagues (2014) stimulated the mice hippocampus with MRI-guided fTUS, and their results showed significance increase in the number of proliferating cells and newborn neurons in the dentate gyrus of the dorsal hippocampus. Another example of a promising brain region might be the basal ganglia to treat disorders involving motor control, such as PD or Tourette's syndrome. While current TPS studies have largely focused on cortical stimulation, exploring the effects of TPS on subcortical structures like the basal ganglia could open new therapeutic pathways for motor and tic disorders.

Beisteiner and colleagues (2020) conducted measurements on human skull and brain samples prior to their first clinical trial to determine the TPS precision capabilities. They found that the transversal resolution was noted to be a few millimeters, while the axial resolution ranged from 60 to 80 millimeters. However, many studies in this review stimulated large brain areas, making it difficult to establish clear causal links between stimulation sites and therapeutic effects. The authors of the included studies adopted this strategy to either focus on the entire condition-related brain regions (e.g., memory network nodes including the DMN, and language networks related to AD), or regions associated with specific conditions that were found significant in the previous studies (e.g., targeting the left dlPFC for ADHD treatment). Future research should investigate smaller, more precisely targeted regions to improve our understanding of region-specific effects. For example, targeting individual hippocampal subfields, such as the dentate gyrus or CA1 region, could offer a more granular understanding of TPS's role in neurogenesis and memory functions. Similarly, precise targeting of the prefrontal cortex subregions (e.g., portions of the dorsolateral vs. ventromedial prefrontal cortex) might clarify the impact of TPS on cognitive

flexibility or mood regulation in disorders like MDD or ADHD. Considering the details of the TPS system in the included studies, the system seems to have a good neuronavigation tool which could easily facilitate this precision, allowing researchers to localize TPS to smaller, more specific areas and better establish the mechanistic relationships between stimulation and observed outcomes.

Emerging research on TPS has suggested its potential to enhance neuroplasticity, but the underlying biological mechanisms remain underexplored. Future studies should investigate the role of growth factors, such as GDNF and BDNF, in TPS-induced tissue and blood vessel regeneration (i.e., neurogenesis and angiogenesis). This could be particularly relevant in neurodegenerative conditions such as AD, or in focal damage such as ischemic stroke, where promoting neural repair and vascular regeneration could have therapeutic benefits. Research could involve combining TPS with biomarker assessments (e.g., serum BDNF/GDNF levels) or advanced neuroimaging techniques (e.g., DTI for assessing white matter integrity) to investigate how TPS modulates these growth factors and whether it translates into functional and structural improvements. Additionally, animal models could be leveraged to conduct histological assessments of neural and vascular growth post-TPS, providing mechanistic insights at the tissue level.

Furthermore, future research should aim to overcome the limitations of current studies, such as small sample sizes, lack of sham controls, and inconsistent outcome measures. RCTs with robust sham controls, larger sample sizes, and multicenter collaborations would enhance the reliability and generalizability of findings. Moreover, more studies with consistent and standardized outcome measures, particularly those related to cognitive functions, motor abilities, and mood regulation, are needed to allow for more rigorous cross-study comparisons and,

potentially, meta-analyses. Neuroimaging and biomarker assessments should also be consistently incorporated into study designs to provide objective evidence of TPS-induced changes at the neural and molecular levels. Furthermore, combining repeated TPS interventions with neuroplasticity-promoting strategies, such as cognitive training or physical exercise, could be explored to maximize clinical benefits. The potential of TPS to synergize with other therapeutic modalities remains underexplored and could be a valuable area for future research.

In summary, by targeting deeper brain regions, focusing on specific neural networks, investigating growth factor expression, and addressing methodological limitations, future studies could significantly advance our understanding of TPS and its therapeutic potential.

5. Conclusion

This review highlights the growing evidence supporting the cognitive enhancement and therapeutic potential of neuronavigated TPS, as a non-invasive neuromodulation technique, covering a range of healthy but also neurological and psychiatric conditions, while also underscoring several critical limitations in the current body of research. Although TPS has shown promise in enhancing neuroplasticity, cognitive function, and motor control, most studies have targeted large brain areas, limiting the ability to draw clear causal relationships between stimulation sites and therapeutic effects. Additionally, even though the existing literature suggests that TPS can stimulate brain regions up to 8 cm from scalp with a transversal resolution of a few millimeters, deeper brain regions remain underexplored, yet they may play pivotal roles in conditions. Future research should prioritize more precise stimulation of smaller, region-specific targets and aim to investigate neural networks as a whole to better understand TPS's network-level

effects. Furthermore, studies focusing on the role of growth factors, such as GDNF and BDNF, in neurogenesis and angiogenesis could shed light on the underlying mechanisms of TPS-induced neurorepair. To address the limitations of small sample sizes and methodological inconsistencies, larger, sham-controlled trials with longer follow-up periods are necessary. Ultimately, these research directions could unlock the full therapeutic potential of TPS, enabling its more widespread and effective application in clinical practice.

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7. Appendices

7.1. Detailed Search Strategy

Search number	Query	Results
12	((((((Transcranial Pulse Stimulation[Title/Abstract]) OR (Pulsed Ultrasound Stimulation[Title/Abstract])) NOT (Transcranial Magnetic Stimulation[Title/Abstract])) NOT (Transcranial Direct Current Stimulation[Title/Abstract])) NOT (TMS[Title/Abstract])) NOT (tDCS[Title/Abstract])) NOT (Transcranial Pulsed Current Stimulation[Title/Abstract])	106
10	Transcranial Pulsed Current Stimulation[Title/Abstract]	43
9	tDCS[Title/Abstract]	7,440
8	TMS[Title/Abstract]	16,405
7	Transcranial Direct Current Stimulation[Title/Abstract]	7,405
6	Transcranial Magnetic Stimulation[Title/Abstract]	20,589
3	Pulsed Ultrasound Stimulation[Title/Abstract]	80
1	Transcranial Pulse Stimulation[Title/Abstract]	28

7.2. Quality Assessment Tools

7.2.1. NIH Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?			
2. Were eligibility/selection criteria for the study population prespecified and clearly described?			
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			
4. Were all eligible participants that met the prespecified entry criteria enrolled?			
5. Was the sample size sufficiently large to provide confidence in the findings?			
6. Was the test/service/intervention clearly described and delivered consistently across the study population?			
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?			
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?			
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?			
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?			
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?			
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			

7.2.2. NIH Quality Assessment of Controlled Intervention Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?			
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?			
3. Was the treatment allocation concealed (so that assignments could not be predicted)?			
4. Were study participants and providers blinded to treatment group assignment?			
5. Were the people assessing the outcomes blinded to the participants' group assignments?			
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?			
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?			
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?			
9. Was there high adherence to the intervention protocols for each treatment group?			
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?			
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?			
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?			
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?			
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?			