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REVIEW

A review of transcranial pulse stimulation: innovations in neuromodulation

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ABSTRACT

Introduction: Non-invasive brain stimulations (NIBS), such as transcranial magnetic stimulation, transcranial direct current stimulation, transcranial alternating current stimulation, transcranial focused ultrasound, and transcranial pulse stimulation (TPS), employ electric currents or acoustic waves to induce and modulate neuroplasticity in humans. Thus, NIBS have the capacity to modify pathological plasticity while promoting plasticity in neuropsychiatric disorders, helping to ameliorate symptoms and enhance rehabilitation.

Areas covered: The efficacy of TPS in treating neuropsychiatric disorders is still unknown; hence, this article reviews the currently available clinical studies on the therapeutic effectiveness of TPS on symptom reduction in the clinical population to inform future neuropsychiatric treatments and research directions.

Expert opinion: The emerging NIBS treatment modality TPS demonstrates promising evidence in modulating symptoms in clinical population of neurocognitive disorders, common mental disorders, and neurodevelopmental disorders. It has been well tolerated across age groups, from adolescents to older adults. Thus, it is essential to encourage future research to investigate the underlying neurophysiological and biochemical effects of TPS, as well as its sustainability, by incorporating high-quality randomized controlled trials with larger sample sizes to strengthen the validation of its effects.

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Non-invasive brain stimulation techniques; transcranial pulse stimulation; neuromodulation; neurorehabilitation; therapeutic intervention

1. Introduction

1.1. Non-invasive brain stimulation (NIBS)

In the late 20s, various treatment methods utilizing non-invasive brain stimulation (NIBS) for neurological and psychiatric conditions have emerged. Different types of NIBS vary based on their unique characteristics (see Table 1).

Transcranial magnetic stimulation (TMS) was initially introduced in the late 1980s [1]. It involves the flow of a brief, extremely high-intensity electric current (several thousand amps) through a copper wire coil, which generates a magnetic field that can reach approximately 2 T and lasts for about 100 μs [2]. With the established research support for its efficacy, TMS is now Food and Drug Administration-approved to treat major depressive disorder and obsessive-compulsive disorder [3,4]. The traditional ring and figure-8 coil designs produce diffuse fields that extend over volumes of several cubic centimeters and decrease exponentially in amplitude from the brain's surface with depth. This limits their effectiveness to the cortical surface. At a depth of 1.5 cm, the lateral spread of the magnetic field exceeds 10 cm^2 [5]. While TMS is considered a safe technique, some stimulation protocols have been linked to discomfort in patients [6].

Soon after, different forms of transcranial electrical stimulation gained popularity in the early 2000s due to its ease of administration and accessibility in enhancing cognitive functions, including emotional processing [7,8], treating treatment-resistant depression [9], anxiety [10], and posttraumatic stress disorder [11], and neurological rehabilitation [12,13], serving as an alternative to traditional treatment modalities. They include a spectrum that ranges from transcranial direct current stimulation (tDCS) to high-frequency alternating current stimulation (tACS) in the kilohertz range. The current flows through the scalp and traverses the extracortical layers to reach the cortex, where it modulates the membrane polarity of the underlying neurons. This process induces changes in the electrical activity of the neurons, which in turn modifies their synaptic efficiencies. Although this alteration does not generate action potentials, it is enough to adjust the response threshold of the stimulated neurons [14,15]. However, these methods suffer from a broadly diffuse electric field that cannot be precisely directed at a specific brain target. While reducing the size of one of the electrodes can enhance focality, it still affects approximately 10 cm^2 of the brain's surface area, where around 50% of the maximum power is applied [16].

Both TMS and forms of transcranial electrical stimulations use direct or induced electric currents. The limitation with electrical stimulation of the scalp may restrict conductivity and a potential inability in accessing deeper brain regions and tissues below the cortical surface due to poor spatial resolution [5,17,18]. In contrast, focused ultrasound (FUS) applies ultrasonic waves, which is the most promising method for stimulating neurons at greater depths without affecting surface brain tissue [19]. FUS is a noninvasive technique for transmitting mechanical forces in lower frequency stimulus within the necessary firing rate range [20]. This allows effective stimulation of neurons cells situated deep within the body via an acoustic pressure wave. This approach can produce a range of biological effects, both thermal and mechanical, contingent on intensity, duration, and pulse width of the delivered ultrasound. The acoustic waves facilitate high focal precision based on the driving frequency (3 mm at 0.5 MHz) wavelength through constructive interference of the incident waves. In other words, it

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Article highlights

- TPS is an emerging technique that applies repetitive, high-pressure, ultrashort shockwave pulses (3 μs duration, repeated every 200–300 ms) within the pulse frequency range to influence neuronal activity in the brain.
- The TPS procedure uses a handpiece equipped with detection lenses, a 3D camera, and patient glasses to precisely target stimulation, while real-time tracking of the handpiece position automatically indicates treated areas and accounts for individual brain characteristics using personalized MRI data.
- TPS overcomes the limitations of conductivity and the inability to reach deep brain regions inherent in existing electric stimulation techniques (TMS, tDCS, and tACS) by using low-intensity, focused shock waves with good spatial precision and resolution.
- Targeting pulses to the dorsolateral prefrontal cortex (DLPFC) and the default mode network (DMN) enhances cognitive functions and reduces depressive severity. Left DLPFC is associated with improved depressive symptoms and attention-deficit/hyperactivity disorder symptoms, while temporoparietal junction is related to improved autism spectrum disorder symptoms.
- TPS is safe and well-tolerated, with reported adverse event rates ranging from 4% to 33.3%, with the most common side effect being a transient headache.

forms a focal spot deep within the tissue; hence, cells closer to the transducer along the propagation path are not affected. Therapeutic ultrasound (US) such as high-intensity FUS, delivering continuous (very long pulse width) ultrasound, was first introduced in the 1950s [21], to treat tremors [22] and cancers [23], by destroying a region of tissue permanently. It was discovered that US at lower intensities can lead to direct neuromodulation of neurons without any tissue destruction [24], hence the introduction of forms of NIBS low-intensity transcranial stimulation that adopted different waveforms, transcranial focused ultrasound (tFUS) and transcranial pulse stimulation (TPS). tFUS adopts ultrasound presented in periodic oscillations with narrow bandwidth. It is evident in alternating from high precision intrinsic oscillation in the beta frequencies to wider cortical areas, resulting in improved spatial and temporal tactile discrimination abilities and enhanced motor performance [25,26]. tFUS is particularly notable for its ability to target not only cortical tissue but also deeper brain structures. Local field potentials recorded with deep brain stimulation lead in the globus pallidus internus provide direct electrophysiological evidence of TUS target engagement and specificity in these deeper areas, emphasizing its potential as a noninvasive DBS strategy for neurological and psychiatric disorders [27]. Despite the comparable lateral resolution of 3–7 mm between the two techniques, the long sonication trains cause tFUS the concern of tissue warming and standing waves that lead to unintended secondary stimulation, liming spatial specify [28,29]. TPS, on the other hand, employs low-intensity, focused shock waves, which are higher in pressure amplitudes that create steepening effect. It has been identified that the TPS system may more effectively avoid hazardous brain heating and secondary stimulation maxima, as well as achieve improved skull penetration due to its lower pulse frequency compared to conventional fTUS [30].

1.2. The mechanism of TPS

TPS is considered one of the most recent advancements in NIBS technology. This mechanism is based on the principles of mechanotransduction. Mechanotransduction is a process in which the forces that emerge at tissue interfaces during momentum transfer, governed by these physical laws through transmission and selective reflection, can cause slight movements at these interfaces. These movements lead to the stretching and deformation of cell layers, temporarily making them permeable to ions and certain molecules [31]. In other words, cells convert mechanism stimuli into biochemical signals, consequently activating essential cellular functions, such as migration, proliferation, differentiation, and apoptosis [32,33]. TPS can enhance the formation of new blood vessels (angiogenesis) and nerve regeneration, stimulate the production of vascular growth factors and brain-derived neurotrophic factor, and improve cerebral blood flow [34]. TPS may modulate neuroplasticity, which enhances cell permeability, triggers mechanosensitive ion channels, and releases nitric oxide, which induces vasodilation, enhances metabolic activity, and supports angiogenesis [35,36]. As brain conditions, such as Alzheimer's disease (AD), are related to functional loss of nerve cells, shock waves to affected areas can modulate transmitter and neurotrophic factor concentrations and enhance neuroplasticity [37].

The important characteristic of shock waves that explains how stimulation can reach deeper regions without affecting surface tissue is because the pressure-related process is too rapid (microsecond range) for physiological process. Thus, within this timeframe, biochemical interchange is possible through opened pores in stretched membranes. When reflection happens at interfaces, shock wave momentum transfer allows accelerations in the masses with slight movements within milliseconds. The forward-directed force effect determines the effect of shock waves that cause interface momentum transfer. As shock waves do not get discontinued in tissue or water, but only in the acoustic impedance, they become ideal means for deep tissue effects without any damage caused to the surrounding tissues.

When applied to the brain, it utilizes repetitive, high-pressure ultrashort shockwave pulses (3 μs, repeated every 200–300 ms) within the ultrasound frequency range to influence neuronal activity in the brain [38] (Figure 1). It now enables three-dimensional targeting of deeper structures within the human brain (i.e. 8 cm into the brain) [39]. TPS is the first ultrasound-based NIBS technique to receive approval for clinical applications (CE mark) and certified as treatment for AD, classified as a Class II medical device (Figure 2).

1.3. Objectives

As TPS is an emerging technique with limited research findings on its therapeutic application, this study is going to review the effectiveness of TPS on different mental illness and neurocognitive disorders. A deeper understanding regarding different TPS intervention protocols will help to inform a clearer future direction for research and development of clinical practice.

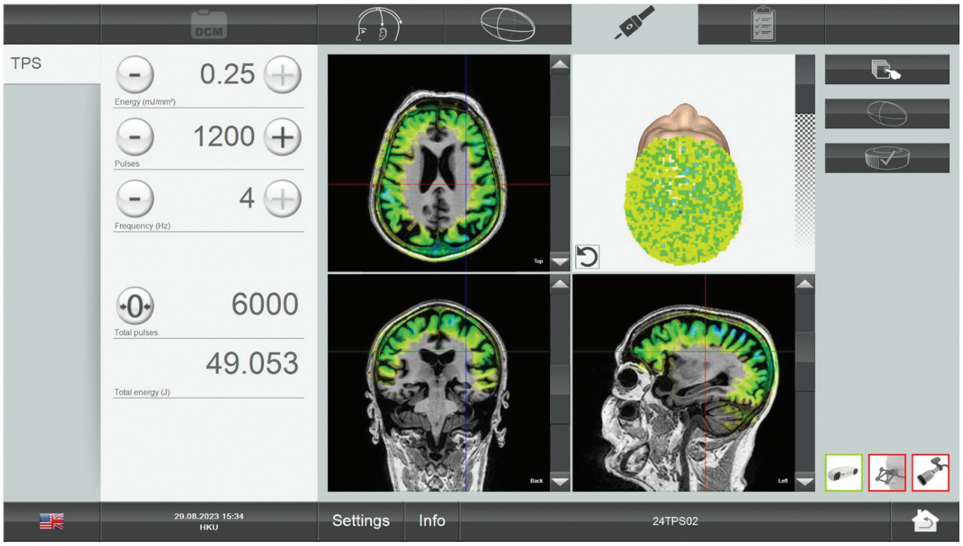
2. The effectiveness of TPS treating neurocognitive disorders, common mental disorders, and neurodevelopmental disorders

In this review, we explore evidence on the effectiveness of TPS in treating a) neurocognitive disorders; b) common mental illness; and c) neurodevelopmental disorders.

Table 1. Types of non-invasive brain stimulation (NIBS).

Non-invasive brain stimulation	Transcranial magnetic stimulation (TMS)	Transcranial electrical stimulation		Transcranial focused ultrasound (tFUS)	Transcranial pulsed stimulation (TPS)
		Transcranial Direct Current Stimulation (tDCS)	**Transcranial Alternating Current Stimulation (tACS)**		
Mechanism	Employs magnetic fields to induce electrical currents directly within neurons, leading to the generation of action potentials.	Applies a constant, low electrical current via electrodes placed on the scalp. This current modulates the resting membrane potential of neurons, modulating neuronal excitability and potentially influencing brain rhythms.	Alternating electrical current at specific frequencies via electrodes placed on the scalp. This current oscillates back and forth, entraining neuronal excitability and potentially influencing brain rhythms.	Applies long trains of ultrasound waves	Applies ultrashort shock waves, varying in parameters, to modulate neuronal activity
Targeting	Highly precise; can target specific cortical areas with focused magnetic pulses.	While it can target specific cortical areas based on electrode placement, it lacks the spatial precision of TMS	While it can target specific cortical areas based on electrode placement, it lacks the spatial precision of TMS	Highly precise; can target specific cortical areas via focused ultrasound beams	Less precise, covers broader areas
Effects on brain activity	Immediate excitatory or inhibitory effects based on stimulation frequency; robust modulation of neuronal firing.	Gradual changes in neuronal excitability; can induce long-lasting effects but typically subtler than TMS.	Can enhance or inhibit neuronal activity based on frequency; may influence brain oscillations and cognitive functions.	Can activate or inhibit neuron activity selectively, reaching deeper brain structure	Effects depend on pulse characteristics; aims for excitatory or inhibitory modulation similar to TMS but with less established protocols. TPS can potentially lead to cumulative effects over time, similar to tDCS, which may benefit long-term interventions.
Versatility in stimulation parameter	Fixed waveform, specific to device settings	Adjustable (typically 1–2 mA)	Adjustable (current amplitude varies)	Adjustable (intensity, pulse duration)	Adjustable (pulse shapes and frequencies varies)
Cost effectiveness	High cost; equipment is expensive and requires specialized facilities.	Generally low-cost; devices are affordable for research and clinical use.	Also low-cost but slightly more complex than tDCS; still affordable for many.	Higher initial cost due to technology requirements	Simplier and more affordable devices; currently more affordable than TMS and tFUS and competitive with tDCS/tACS.
Accessibility	Limited accessibility due to cost and the need for trained personnel.	Widely accessible; devices are portable and easy to use.	Accessible but requires some training for optimal use.	Less common in clinical setting	Potentially high accessibility; devices may be simpler and portable.
Safety and side effects	Discomfort or pain at the stimulation site; headaches; transient changes in mood or cognition; rare cases of hearing loss with improper coil use.	Mild, transient effects such as tingling, itching, or discomfort at the electrode site; headaches; fatigue; nausea (rare).	Similar to tDCS, with mild sensations at the electrode sites; potential for transient changes in mood or cognitive performance.	Some concerns over potential thermal effects, require careful monitoring. Potential for mild sensations similar to tDCS.	Potential for mild sensations similar to tDCS; uncommon reports of discomfort.

This table summarizes various NIBS techniques, including TMS, tES, tFUS, and TPS. For each technique, the mechanism of action, targeting precision, effects on brain activity, versatility in stimulation parameters, cost-effectiveness, accessibility, and safety profiles are illustrated. Key differences highlight the unique advantages and limitations of each method in clinical and research settings.



Energy (mJ/mm²) 0.25

Pulses 1200

Frequency (Hz) 4

Total pulses 6000

Total energy (J) 49.053

Figure 1. Documentation of the applied energy and the course of treatment. The energy applied is shown in color, with a display of personal MRI data in three perspectives.

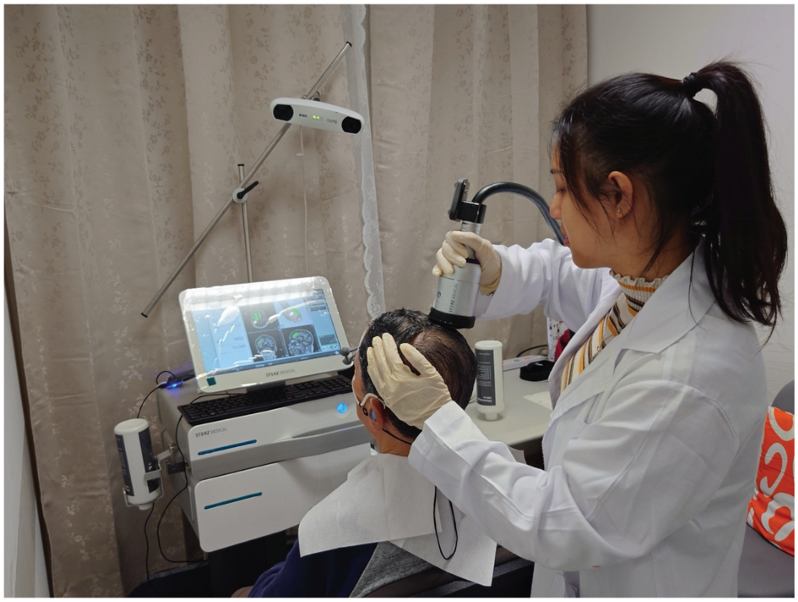


Figure 2. Real-time tracking of the handpiece position automatically indicates which areas have been treated. By utilizing personalized MRI data, individual brain characteristics can be accounted for. Whenever the handpiece position changes, the target regions in the loaded MRI images are automatically updated.

2.1. *The effectiveness of TPS on treating neurocognitive disorders*

The first report of shock wave brain stimulation in clinical population was presented by Beisteiner et al. (2019) for judging safety and preliminary clinical efficacy (see Table 2) [40]. The pilot study applied focused navigated TPS on 35 older patient with AD in an uncontrolled, open-label study. The stimulation targeted AD-affected areas, including the dorsolateral prefrontal cortex and areas of the memory (including default mode) and language networks. Functional magnetic resonance imaging (fMRI) resting state data revealed enhanced functional connectivity in the hippocampus, parahippocampal cortex, parietal cortex, and precuneus. These increased functional connectivity values were significantly associated with CERAD scores, suggesting that the upregulation of the memory network is linked to cognitive performance and improved verbal abilities, an effect that was maintained at 3-month follow-up. In addition, it was found that patients have reduced depressive symptoms post-stimulation and sustained for up to 3 months. In contrast, FIGURAL performance of unstimulated areas, such as occipital-parietal cortex, for visuospatial processing declined. The findings gave ground-breaking evidence of the high focal specificity and precision of TPS in treatment efficacy. However, the limitation of the study is the absence of a sham-controlled comparison group to confirm the stimulation effect. A similar setup targeting AD-affected areas was found to be associated with morphological change, with a reduced cortical atrophy in the left superior parietal lobule and left precuneus in patients with mild AD [41]. In Dorl et al.

Table 2. The effectiveness of TPS on treating neurocognitive disorders, common mental disorders, and neurodevelopmental disorders.

Studies	Country	Clinical Sample	Study Characteristics	Duration of the Course	Session Frequency	Session Duration	Pulse per Session	Energy Used	Targets	Main Findings
Neurocognitive disorders										
Beisteiner et al. [52]	Austria	35 older adult patients with AD	Open-label, uncontrolled, multicentric	Two to four weeks	3 sessions per week	NA	6000 (5 Hz pulses per second)	0.2 mJ mm – 2,	DLPFC, DMN	Improved cognition scores (CERAD) maintained at 3 months,reduced depressive symptoms (BDI-II, GDS).Upregulation of memory network in task based and resting state fMRI
Popescu et al. [41]	Austria	17 older adult patients with AD	Follow-up study; open-label, uncontrolled	Four weeks	NA	NA	6000 (5 Hz pulses per second)	0.2 mJ mm – 2	DLPFC, DMN	Neuropsychological changes (CERAD) were correlated with increased cortical thickeness after TPS.
Dorl et al. [42]	Austria	18 older adult patients with AD	Follow-up study; open-label, uncontrolled	Four weeks	3 sessions per week	NA	6000 (5 Hz pulses per second)	0.25 mJ/mm2	DLPFC, DMN	Correlation between visuo-constructive score changes and functional connectivity and in the untargeted visuo-constructive network. Decreased visuo-constructive capabilities 3 months post-stimulation.
Matt et al. [43]	Austria	18 older adult patients with AD	Follow-up study; open-label, uncontrolled	Three days	3 sessions on 3 consecutive days	4 mins		0.25 mJ/mm2	DLPFC, DMN	Reduction of depressive symptoms (BDI-II). Normalisation of the functional connectivity between the salience network and the ventromedial network
Cont et al. [45]	Germany	11 older adult patients with AD	Open-label, uncontrolled, retrospective	Two weeks	a) 3 sessions per week b) 1 session per day	NA	a) 6000 or b) 3000 (4 Hz pulses per second)	0.20 mJ/mm2	DLPFC, DMN, temporal cortex	Improved cognition scores (ADAS, ADAS-Cog) immediately post treatment
Fong et al. [46]	Hong Kong	19 older adult patients with mild NCD	Open-label, uncontrolled	Two weeks	3 sessions per week	NA	6000 (4–5 Hz pulses per second)	0.20–0.25 mJ/mm2	Global stimulation	Improved cognitive scores (MoCA, Verbal Fluency,Stroop interference) and IADL, maintained at 3 months. No change in serum BDNF level.
Common mental disorders										
Cheung et al. (2023)	Hong Kong	30 adult patients with MDD	Waiting list control group, single-blind	Two weeks	3 sessions per week	30 mins	300 (4–5 Hz pulses per second)	0.20–0.25 mJ/mm2	Left DLPFC	Significant improvements of depressive symptoms (HDRS-17), anhedonia (SHAPS), IADLs, and cognitive performance (MoCA, digit span, trail making test), effect sustained at 3 months post-stimulation.
Neurodevelopmental disorders										
Cheung et al. (2023)	Hong Kong	34 adolescent patients with ASD	Sham-controlled, parallel-group, double-blind	Two weeks	3 sessions per week	30 mins	300 (4–5 Hz pulses per second)	0.20–0.25 mJ/mm2	Right temporoparietal junction	Significant improvement in the severity of clinical symptoms (CARS, CGI)
Cheung et al. [50]	Hong Kong	30 adolescent patients with ADHD	Sham-controlled, parallel-group, double-blind	Two weeks	3 sessions per week	30 mins	800 (4 Hz pulses per second)	0.25 mJ/mm2	Left DLPFC	Significant improvement in the severity of clinical symptoms (SNAP-IV) maintained at 1 and 3 months postintervention

This table compares studies examining the effects of TPS on various neurocognitive, common mental, and neurodevelopmental disorders. Main findings consistently indicate improvements in cognitive function and reductions in depressive symptoms, with effects often maintained for several months post-treatment. Notably, studies involving younger patients with neurodevelopmental disorders also report significant improvements in clinical symptoms.

(2022)'s study, the findings revealed a negative correlation between visuo-constructive score changes and functional connectivity and in the untargeted visuo-constructive network, which aligned with the natural progression of the disease in older adults with AD [42]. While the aforementioned studies found supporting evidence for high focal precision nature of TPS techniques in the AD-related areas, Matt et al. (2022) found that upon stimulation in the extended dorsolateral prefrontal cortex (DLPFC), alleviated depressive symptoms in AD patients was implicated by reduced functional connectivity between the ventromedial network (left frontal orbital cortex) and the salience network (right anterior insula) [43,44]. The finding offers an additional option to the current state-of-the-art treatments for AD patients with depressive symptoms.

Although some studies have reported improvements in AD-specific domains following stimulation, there is limited knowledge about whether patients at all stages of cognitive impairment (both severe and mild AD) would benefit from this stimulation. A subgroup analysis revealed that TPS had a greater effect in patients with moderate and severe cognitive impairments as compared to those with mild cognitive impairment [45]. Similarly, Cont et al. (2022) also suggested supportive evidence of improved depressive symptoms, reflected by the ADAS affective score for treating depressive symptoms in AD patients with TPS [45]. However, it is worth noting that the sample size was limited ($N = 11$), which requires future studies with a larger sample to validate the finding.

Consistent improvement was found in the global cognition of AD patients across different TPS interventional studies despite the differences in cognitive measures. While most studies adopted CERAD to measure cognitive abilities of AD patients, Fong et al. (2023) applied different measures, including MoCA for global cognition and other measures such as digit span, the Stroop test, Verbal Fluency Test, and the Trail making test that assess executive functions in a clinical population with mild NCD, not limited to AD [46]. The study revealed improvements in the global cognition of patients with NCD and improvements in executive function, as indicated by better performance in Stroop interference. A trend toward reduced depressive symptoms and apathy was also noted post-intervention.

2.2. *The effectiveness of TPS on treating common mental disorders*

There is only one study that explored the effect of TPS on mental disorders with a waitlist control group. Cheung et al. (2023) applied TPS focusing on the left DLPFC on 15 adult patients with Major Depressive Disorder, while the remaining participants were assigned to the treatment-as-usual group [47]. Significant improvements were revealed in their depressive symptoms, anhedonia, daily functioning, global cognition, and executive functioning post-stimulation, with effects maintained after 3 months. This study provided supportive evidence that improvements in depressive symptoms may result in enhanced cognition, attention, memory, and executive function, as well as a reduction in anhedonia symptoms [48].

2.3. *The effectiveness of TPS on treating neurodevelopmental disorders*

There are limited studies available exploring the effect of neuromodulation via TPS on neurodevelopmental disorders. Cheung et al. (2023) conducted a double-blind, sham-controlled study that demonstrated improvements in core autism spectrum disorder (ASD) symptoms by targeting the right temporoparietal junction in a group of 32 adolescents with ASD [49]. The effect of TPS was significant in reducing core ASD symptoms immediately after stimulation, with improvements sustained at 3 months. This is supported by the improved ASD symptoms rated by behavioral measures, with convergent consensus between clinician-rated measures (i.e. CGI) and parent-reported core symptoms (i.e. CARS). While pulse stimulation to 15 adolescents with ADHD on the left DLPFC showed significantly improved ADHD symptoms post-stimulation and maintained at 3 months compared to those without TPS [50]. Adolescents in the TPS group reduced ADHD severity, measured by SNAP-IV scores, in inattention, hyperactivity/impulsivity, and oppositional defiance twice as much as the sham-control group.

2.4. *Adverse effect and safety of TPS*

Regarding the safety and adverse events evaluating efficacy of TPS on NCD studies, only two studies, 4% of the participants each [40,45] reported infrequent adverse events (i.e. painless pressure sensations, pain, headache, nausea, and drowsiness) that subsided within 1 day. In the study regarding patients with Major Depressive Disorder (MDD), also 4% of participants reported transient headaches [47]. One-third of the participants in the study evaluating ASD adolescents and one-fifth of those ADHD adolescents reported transient headache and pains [49,50].

3. Discussion

This review examines the evolution of NIBS and the development of TPS. Since TPS is an emerging technique, it is paramount to elucidate its therapeutic effect on clinical population to inform further development and research direction. Studies in this review have shown that TPS significantly improved cognitive function in NCD, depressive symptoms in MDD and core symptoms of neurodevelopmental disorders.

Regarding the neuromodulation in NCD patients, the studies in this review identified common stimulation targets in the DLPFC and DMN. As the DMN is a region recognized for its crucial role in cognitive function and memory in AD, and it begins to degenerate early in the progression of the condition [51], it becomes a common focused region for stimulation. These studies emphasized the therapeutic benefits related to cognitive enhancement in AD and a broader population of older adults with NCD. Additionally, some studies noted a reduction in depressive symptoms [40,43,45] and sustained cognitive improvements in those with follow-up assessments at 3 months [46,52]. These cognitive enhancements were reflected in improved scores on various cognitive assessments, such as, the CERAD test battery, MoCA, MMSE, and ADAS-cognitive, as well as affective measures, such as ADAS-affective, BDI, and GDS. Neuroimaging findings further indicated that changes in functional connectivity and cortical thickness in patients with AD and/or NCD are associated with post-stimulation improvements in cognitive and emotional functioning.

Since the use of TPS also alleviated depressive symptoms in AD patients, further research into neuromodulation investigated the impact of TPS on adults with MDD specifically. With a focus on alleviating depressive symptoms, the target of stimulating left DLPFC has shown immediate and sustained improvement in depressive, anhedonia, daily functioning, global cognition, and executive functioning in adults with MDD [47]. This effect is consistent with previous research suggesting that hypoactivity in the left DLPFC is associated with negative emotional judgments [9,53]. Avissar's (2017) study reported consistent findings, indicating that reduced functional connectivity was linked to a decrease in depressive severity following rTMS at the same stimulation target [54]. This indicates that TPS may provide a relatively cheaper and easier-to-administer alternative as a form of NIBS for treating individuals with depression or treatment-resistant depression.

TPS initially targeted the older population to modulate neurodegenerative systems and has since been extended to younger individuals with neurodevelopmental conditions that could benefit from neuromodulation. Cheung and colleagues' research is among the first studies to explore the efficacy of TPS in adolescents with ASD and ADHD, respectively, [49,50]. Existing research indicates that the right temporoparietal junction is a crucial neural marker for moral judgment and decision-making, which are clinical characteristics of ASD related to their distinct theory of mind abilities [55]. While rTMS stimulation of the same region was associated with improved social communication, Cheung's (2023) study showed improved clinical symptoms including relating to people, emotional response, object use, adaption to change, listening response, fear of nervousness, verbal communication, level of consistency of intellectual response and general impression, with specific communication and sensory subsets sustained for 3 months post-stimulation [49]. This has offered an alternative treatment option compared to conventional pharmacological therapies, which primarily focus on symptomatic control of associated comorbidities rather than addressing core deficits [56]. Additionally, conventional behavioral treatments can also be time-consuming.

Another neurodevelopmental condition evaluated for the effectiveness of TPS is ADHD. Cheung's (2024) study revealed that adolescents in the TPS group reduced ADHD severity in inattention, hyperactivity/impulsivity, and oppositional defiance twice as much as the sham-control group [50]. Compared to other NIBS with the same stimulation target at the left DLPFC, Sotnikova's (2018) study showed that applying tDCS over the left DLPFC on adolescents with ADHD was associated with improved attention, working memory, cognitive flexibility, and response inhibition [57]. The same effect on working memory and executive function was not found in Cheung's (2024) study with the application of TPS [50]. Possible reasons for the null effect may include the influence of pharmaceutical input and the relatively mild symptom severity in the sample, which might allow for an effect to be detected with a longer interval after stimulation. Typical pharmacological treatment of ADHD includes stimulant (i.e. methylphenidate) and nonstimulant (atomoxetine), which focus on modulating the dopaminergic and noradrenergic systems in the frontal cortex, as well as the dopaminergic system in the basal ganglia [58]. Another line of treatment includes psychosocial intervention [59]. Therefore, the development of TPS may allow add-on treatment for adolescents with ADHD on top of the conventional treatment modalities.

This review provides evidence for the safety of TPS, reporting transient headache as the most common side effect among nine studies. The reported adverse events range from 4% to 33.3%, which provide promising evidence that TPS is safe as a therapeutic modality for clinical applications across adolescents to older adults.

3.1. Limitations

Although there is substantial evidence supporting the effectiveness of TPS in enhancing cognitive abilities, the uncontrolled, open-label design of these studies limits the validity of the findings. The absence of a control or sham-control group suggests that the effects of neuromodulation may not be solely attributable to TPS. Furthermore, not all studies provide detailed information on the number of pulses and duration of intervention sessions, making it difficult to effectively replicate or compare findings across different intervention designs or accurately assess the effects of TPS. The most common TPS procedure applies 3 μs, 0.2 mJ/mm^2 energy flux density, and pulse repetition frequency 4–5 Hz. The most common duration of TPS treatment was 2–4 weeks, three sessions per week. With a wide variation in the number of pulses per session, ranging from 300 to 6000 pulses per session, it leads to the question whether the number of pulse per session will affect the effectiveness and responsiveness to TPS of the clinical population [60].

Regarding Cheung's (2023) study evaluating the effects of TPS on adults with MDD [47], the relatively young sample, with an average age of 38.8 years and a predominance of females (73%), presents opportunities for further research into therapeutic applications across diverse mental health populations and potential differential effects based on subgroups such as gender and age. Similarly, given the absence of reported severe adverse events, studies investigating the effects of TPS on neurodevelopmental disorders in adolescents have expanded therapeutic options. Further replication of these studies with larger sample sizes, along with neuroimaging evidence, would be beneficial.

4. Expert opinion

The integration of TPS into clinical practice opens new avenues for existing treatment methods. As mentioned earlier, TPS promotes changes in neuronal activity and supports neural growth and repair [34]. This addresses the gap in existing treatments that may be less effective for certain mental disorders, particularly neurodegenerative and neurodevelopmental conditions. Compared to other NIBS, TPS offers the advantage of high precision and, most importantly, utilizes shock waves to target deeper tissues or brain region [18]. This includes areas such as the hippocampus, which is crucial for memory and learning, and amygdala, which is involved in emotional regulation [61]. In addition, TPS requires fewer session than conventional NIBS to achieve comparable outcomes [6,62,63]. As a result, the treatment burden on patients is reduced, potentially enhancing both acceptance and completion rates of the treatment.

Advances in TPS could significantly impact diagnosis, treatment guidelines, and drug utilization. By better targeting treatment, TPS could lead to more personalized approaches, optimizing therapeutic outcomes and reducing healthcare costs. However, realistic implementation into clinical practice faces several barriers, including regulatory hurdles that require extensive validation of TPS's safety and efficacy. Clinicians also need specific training to effectively implement TPS, which may not be readily available in all healthcare settings. Financial factors, including reimbursement policies and the cost of the technology, may further hinder widespread adoption.

Despite its promise, TPS encounters several challenges. Our review highlighted the variability in treatment parameters, such as session frequency, duration, pulse frequency, and energy levels, across studies, which complicates comparisons of effectiveness and raises questions about optimal treatment protocols. There is also a limited understanding of the mechanisms underlying TPS. While studies indicate behavioral changes, there is a gap in understanding the neurochemical changes induced by TPS, necessitating research into how TPS affects neurocognitive disorders at a biochemical level. Addressing these challenges requires high-quality RCTs with larger sample sizes and extended follow-up periods. Incorporating neuroimaging and blood biomarkers, such as BDNF and inflammatory markers, could provide deeper insights into the biochemical changes caused by TPS.

The future of TPS holds considerable potential for further research. Understanding the medium- and long-term effects of TPS and identifying factors that contribute to treatment sustainability are vital areas for exploration. The ultimate goal is to establish TPS as a recognized and effective treatment modality for various neurological and psychiatric conditions, potentially altering the landscape of mental health treatment. As research progresses, it is essential to consider whether the future of study lies solely in TPS or if other promising areas are emerging. Innovations in brain stimulation techniques, neuroimaging, and biomarkers may offer complementary avenues for advancement.

In the next 5 to 10 years, the field is likely to evolve significantly. We may see the standardization of protocols, establishing clear guidelines regarding optimal treatment parameters to enhance consistency and effectiveness. TPS could be combined with pharmacological treatments or psychotherapeutic approaches to boost outcomes, allowing for more tailored treatment strategies. Overall, the evolution of TPS and related technologies could lead to more effective, efficient, and accessible mental healthcare, addressing both current limitations and future needs in the field.

Abbreviations

AD	Alzheimer's disease
DLPFC	Dorsal Lateral Prefrontal Cortex
DMN	Default mode network
CERAD	Consortium to Establish a Registry for Alzheimer's Disease) Neuropsychological Assessment Battery
BDI-II	Beck's Depression Inventory
GDS	Geriatric Depression Scale
ADAS-Cog	The Alzheimer's Disease Assessment Scale-Cognitive
NCD	Neurocognitive Disorder
MoCA	Montreal Cognitive Assessment
IADL	Instrumental activities of daily living
BDNL	Blood levels of brain-derived neurotrophic factor
MDD	Major Depressive Disorder
HDRS-17	Hamilton Depression Rating Scale
SHAPS	Snaith-Hamilton Pleasure Scale
ASD	Autism Spectrum Disorder
CARS	Childhood Autism Rating Scale
CGI	The Clinical Global Impression Scale
ADHD	Attention Deficit/ Hyperactivity Disorder
SNAP-IVI	Swanson, Nolan, and Pelham Teacher and Parent Rating Scale

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