ISSN (Print) 1226-1750
ISSN (Online) 2233-6656
Journal of Magnetics 30(4), 628-637 (2025) https://doi.org/10.4283/JMAG.2025.30.4.628

Efficacy of Temporal Interference Stimulation in Human Studies: A Systematic Review

Chaeyoung Lee[1], Seungmin Hwang[2], Hae Yean Park[3], and Young-Jin Jung[2,4]*

[1]*Department of Occupational Therapy, Yonsei University, Wonju 26493, Republic of Korea*
[2]*Department of Biomedical Engineering, Chonnam National University, Yeosu 59626, Republic of Korea*
[3]*Department of Occupational Therapy, College of Software and Digital Healthcare Convergence, Yonsei University, Wonju 26493, Republic of Korea*
[4]*School of Healthcare and Biomedical Engineering, Chonnam National University, Yeosu 59626, Republic of Korea*

(Received 2 July 2025, Received in final form 5 November 2025, Accepted 5 November 2025)

Temporal interference stimulation (TIS), a noninvasive neuromodulation method based on electromagnetic waves, enables selective stimulation of deep brain regions through the interference of high-frequency electrical currents. This systematic review evaluated the efficacy and safety of TIS and included studies that directly applied stimulation to human participants and achieved functional or behavioral outcomes. A comprehensive database search across Embase, IEEE Xplore, PubMed, and Web of Science identified 23 eligible studies (852 participants in total) published between 2017 and March 2025. Most studies involved healthy adults, while others targeted individuals with obstructive sleep apnea, major depressive disorder, Parkinson's disease, essential tremor, and traumatic brain injury. These studies reported consistent improvements in motor performance domains, such as reaction time, movement accuracy, and motor learning. Furthermore, improvements in cognitive function were observed, particularly in working memory and spatial navigation, although the results varied due to differences in stimulation protocols and assessment tasks. Most studies reported TIS to be safe, with minimal adverse effects primarily limited to skin irritation and no serious neurological or psychological complications. TIS holds considerable potential as a clinical intervention. However, future research should prioritize standardized stimulation protocols, long-term follow-up, and investigations across diverse neurological and psychiatric patient populations to better establish its efficacy and generalizability.

Keywords : temporal interference stimulation (TIS), neuromodulation, human studies, noninvasive brain stimulation, deep brain stimulation, systematic review

1. Introduction

In recent decades, neuromodulation technology, a therapeutic approach for neurological disorders and functional impairments, has seen rapid advancements [1]. Neuromodulation refers to targeted modulation of neural circuit activity via electrical or pharmacological interventions to modulate the behavior of abnormal neural pathways [2]. In particular, deep brain stimulation (DBS) involves surgical implantation of electrodes deep within the brain, followed by continuous electrical stimulation to regulate abnormal neural circuit activity [3]. DBS has proven effective in treating various intractable neuropsychiatric disorders, such as Parkinson's disease (PD), essential tremor (ET), and obsessive–compulsive disorder, and is widely used in clinical practice [4]. However, DBS exerts adverse effects, such as infection, intracranial hemorrhage, mood changes, increased impulsivity, and cognitive decline [5, 6].

Consequently, safer and noninvasive neuromodulation technologies have recently attracted considerable attention [7]. Noninvasive brain stimulation (NIBS) techniques deliver stimulation through the skull to modulate brain function. Examples of these techniques are transcranial magnetic stimulation, transcranial direct current stimulation, and transcranial alternating current stimulation [8]. Owing to their advantages, such as favorable safety profile and reproducibility, these technologies are actively researched

*Corresponding author: Tel: +82-61-659-7366
Fax: +82-61-659-7369, e-mail: yj@jnu.ac.kr

and clinically applied not only to treat various diseases but also to enhance cognitive enhancement and motor rehabilitation [9]. However, existing NIBS methods face a technical limitation: the stimulation current rapidly attenuates once it passes through physiological barriers, such as the skull and cerebrospinal fluid, rendering stimulation insufficient for subcortical targeting [10]. Consequently, the stimulation effect is mainly confined to the cortical surface, which imposes substantial limitations on the noninvasive and precise stimulation of deep brain regions [11].

In 2017, Grossman *et al.* [11] proposed temporal interference stimulation (TIS) to address the aforementioned limitations. TIS involves the delivery of two or more high-frequency alternating currents (several kHz) to the brain through different electrode pairs, thereby inducing actual stimulation from a low-frequency electric field created by frequency interference in the deep brain, corresponding to frequency difference (Δf) [12]. The high-frequency components remain subthreshold for neural activation, whereas the low-frequency envelope induced by interference reaches activation thresholds in deep regions. Theoretically, TIS is expected to be a groundbreaking technology that can noninvasively stimulate deep brain regions while minimizing effects on superficial tissues, complementing the limitations of existing DBS and NIBS.

Current TIS research has mainly focused on animal models or computational magnetic field simulations [13]. Particularly, physiological studies involving rodents and simulation studies based on brain anatomy have theoretically demonstrated the stimulation characteristics and electric field distribution of TIS, as well as its potential for deep stimulation [14].

The fundamental differences in anatomical structure, brain size, tissue conductivity, and neural cell responses between mice and humans [15] have posed inherent limitations in the direct generalization of animal study results to humans. Thus, it is imperative to assess of the safety and efficacy of TIS is essential to determine its clinical applicability, focusing on studies that have applied stimulation to human subjects.

This systematic review evaluated the clinical potential of TIS and included only studies that have directly applied TIS to humans. This systematic review aims to evaluate the clinical efficacy, safety, and applicability of TIS by analyzing human studies in terms of stimulation parameters, outcome measures, and reported side effects.

2. Method

This study evaluated the clinical efficacy and safety of directly applied TIS in human participants. Four electronic databases, namely, Embase, IEEE Xplore, PubMed, Web of Science, were comprehensively searched for studies published in peer-reviewed international journals from January 2017 (when TI was first introduced by Grossman *et al.* [11]) to March 30, 2025. The search terms ‘temporal interference’ OR ‘temporally interfering’ were applied to titles, abstracts, and keywords.

Inclusion criteria were: (1) use of TIS as an experimental intervention, (2) direct stimulation applied to human subjects, (3) full-text availability, and (4) publication in English. The exclusion criteria were studies (1) unrelated to TIS or using the term “temporal interference” in a context different from the neural stimulation method proposed by Grossman *et al*. [11] (e.g., signal processing), (2) conducted on nonhuman subjects (e.g., animal studies), (3) focusing on computational modeling, (4) involving simulations based on human MRI data without

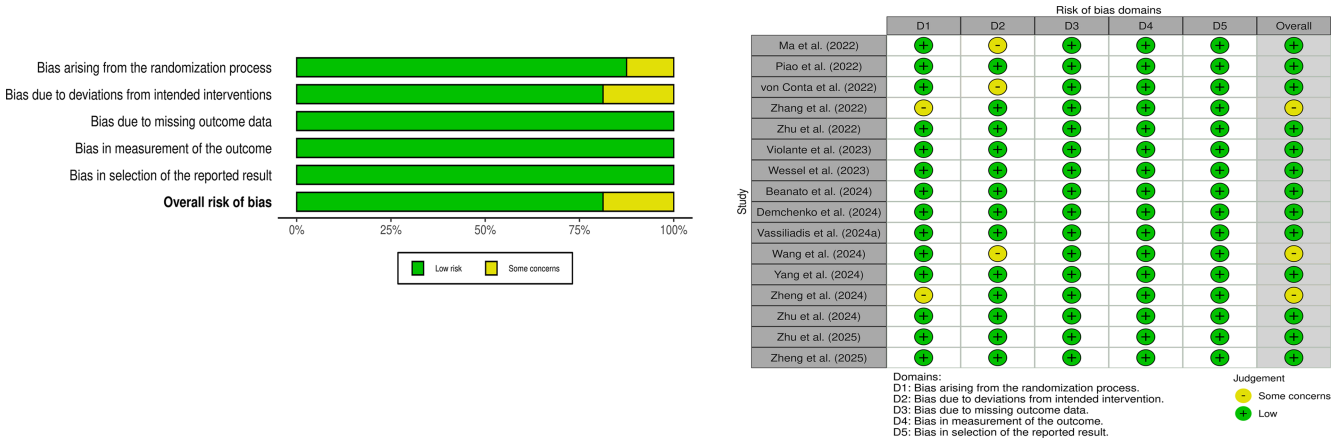

Fig. 1. (Color online) Risk of Bias 2 (RoB 2) Assessment.

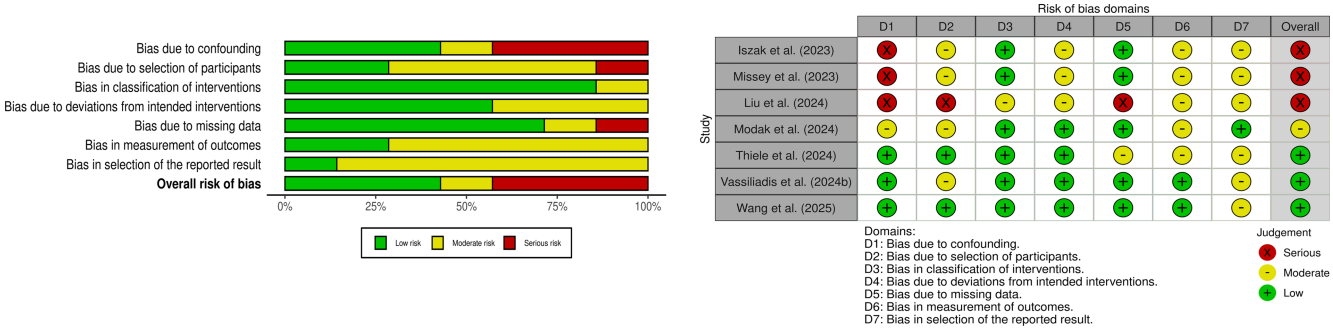

Fig. 2. (Color online) Risk of Bias Non-randomized Studies – of Intervention (ROBINS-I) Assessment.

actual stimulation, (5) involving cadaveric specimens, (6) classified as review articles, (7) providing only an abstract without full-text availability, or (8) that were not peer-reviewed.

In this study, literature selection was performed by first collecting articles through a database search, followed by the removal of duplicate records, title and abstract screening, and full-text review.

The level of evidence was assessed using a five-tier evidence-based practice model [16], where higher levels indicate weaker evidence [17]. Level I includes systematic reviews, meta-analyses, and randomized controlled trials; level II, nonrandomized two-group or cohort studies; level III, prepost and single-group nonrandomized studies; level IV, single-subject experimental designs and survey studies; and level V, case studies and qualitative research. Additionally, for the 16 included Randomized Controlled Trials (RCTs), the risk of bias was assessed using the Cochrane Risk of Bias tool 2.0 (RoB 2). For the 7 included non-randomized studies, the Risk Of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool was used. The assessment was conducted independently by two researchers, with disagreements resolved through discussion. The results are summarized in Fig. 1, 2.

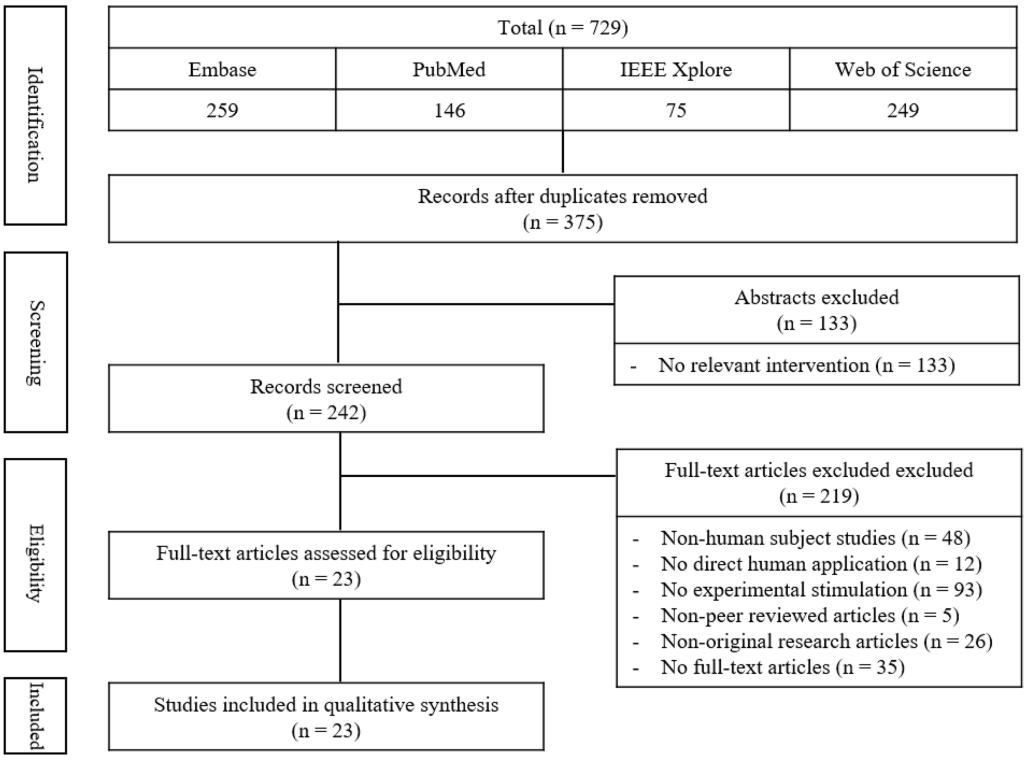

Fig. 3. Flow diagram for the study selection.

3. Results

3.1. Result analysis

An initial database search identified 729 articles. After the removal of 354 duplicate records, 375 unique articles remained. A total of 133 studies were excluded for not applying TIS as a neuromodulation technique or for using the term 'temporal interference' in unrelated contexts, such as signal processing or imaging. The remaining 242 articles underwent detailed full-text review. Application of the inclusion and exclusion criteria led to the exclusion of an additional 219 articles. Finally, 23 articles were included in the systematic review. The study selection process is illustrated in Fig. 3.

Table 1. Classification of evidence level.

Evidence Level	Definition	Frequency n (%)
I	Systematic reviews Meta-analysis Randomized controlled trials	16 (69.57)
II	Nonrandomized two-group study Cohort studies	1 (4.35)
III	Nonrandomized one-group studies Pretest–posttest designs	4 (17.39)
IV	Single experimental studies	1 (4.35)
V	Case studies Qualitative studies	1 (4.35)
	Total	23 (100)

3.2. Characteristics of the included studies

1) Study quality

Among the 23 selected studies, level I evidence accounted for the largest proportion (n = 16, 69.57%), followed by level III papers (n = 4, 17.39%). Levels II, IV, and V accounted for one paper each (4.35%) (Table 1).

2) General characteristics of the study participants

The selected studies included a total of 852 participants. Majority of the studies (n = 19) focused on experiments involving healthy adults, whereas the remaining ones targeted specific patient populations, including those with obstructive sleep apnea (OSA), major depressive disorder

Table 2. Characteristics of the analyzed studies.

Study	N (EG/CG)	Participants	Intervention	Comparison	Task	Outcome
Ma *et al.* (2022) [17]	21/29	Healthy adults	TIS	Sham	RRTT SRTT	Reaction time (RT) (+) Motor cortex excitability (input–output slope) (+) Implicit motor learning (first implicit learning, FIL) (+)
Piao *et al.* (2022) [18]	19/19	Healthy adults	TI-tACS	Sham	N/A	Neurological function (NSE) (N/C) Cognitive function (MoCA) (N/C) Psychomotor function (A-CalCAP) (N/C) Motor function (Purdue Pegboard test, PPT) (N/C) Mood state (VAMS-R) (N/C) EEG (N/C) Adverse effects (AEs) (N/C)
von Conta *et al.* (2022) [19]	34	Healthy adults	tTIS	tACS/HF control	Visual change detection task	Parieto-occipital alpha power (N/C) Beta band power (N/C) Theta band power (N/C) Task performance (N/C) Adverse effects (AEs) (N/C)
Zhang *et al.* (2022) [20]	18/18/8/10	Healthy young adults	TIS	TI/tACS sham	N-back tasks	Working memory (RT, IES in 3-back) (+) Side effects (N/C) Blinding efficacy (N/C)
Zhu *et al.* (2022) [21]	40	Healthy young adults	TI	tDCS	N/A	Functional connectivity between the M1 and secondary motor cortex (+) Side effects (N/C)
Iszak *et al.* (2023) [22]	20/10/10	Healthy adults	TI	tACS/carrier/sham	N/A	Muscle activation (twitches) (+) Phosphene perception (N/C) Alpha power (EEG) (N/C) Side effects (N/C)

Table 2. Continued.

Study	N (EG/CG)	Participants	Intervention	Comparison	Task	Outcome
Missey *et al.* (2023) [23]	12	OSA patients	bTI	Baseline	N/A	Apnea–Hypopnea Index (AHI) (+) Sleep time at SaO_2 <90% (N/C) Adverse effects (AEs) (N/C)
Violante *et al.* (2023) [24]	21	Healthy adults	TIS	Sham	Face-name paired associative task	Memory performance (+) Reaction time (N/C) Confidence rating (N/C) Side effects (N/C)
Wessel *et al.* (2023) [25]	15/15 (young/old)	Healthy young adults and older adults	tTIS	HF control	Sequential finger-tapping task	Motor performance (older adults) (+) Motor performance (young adults) (N/C) Retention performance (90 min, 24 h) (N/C) Resting-state EEG (N/C) Side effects (N/C)
Beanato *et al.* (2024) [26]	30	Healthy young adults	tTIS (iTBS, cTBS)	Control (HF/ tTIS / Sham)	Six blocks of a VR spatial navigation task	Departure time (+) Distance error (N/C) Navigated distance (N/C) GCLR in EC (+) Hippocampal BOLD-departure correlation (+) Side effects (N/C)
Demchenko *et al.* (2024) [27]	15/15	Adults with MDD	tTIS	Sham	N/A	Severity of depression (HAMD-17) (+) sgACC BOLD signal (+) Functional connectivity (sgACC-DMN) (+) Resting-state EEG (N/C) Side effects (N/C)
Liu *et al.* (2024) [28]	3	Patients with PD or ET	TIS	tACS (1 patient)	N/A	Resting tremor severity (MDS-UPDRS- Ⅲ) (+) Other motor symptoms (MDS-UPDRS- Ⅲ) (N/C) Side effects (N/C)
Modak *et al.* (2024) [29]	16	Healthy adults	TIS	Sham	N/A	BOLD activation in OFC (+) BOLD activation in the parahippocampal gyrus (+) No activation of the left caudate (N/C) Side effects (N/C) Negative affect (+)
Thiele *et al.* (2024) [30]	16/18/14	Healthy adults	tTIS	tACS/Sham	A Shepard mental rotation task	Alpha ERD (mental rotation) (+) Resting alpha power (N/C) Mental rotation accuracy (N/C) Mental rotation reaction time (N/C) Side effects (N/C)
Vassiliadis *et al.* (2024) [31]	24	Healthy adults	tTIS (80 Hz)	tTIS (20 Hz) / Sham	Force-tracking motor learning with reinforcement	Reinforcement learning benefit (tTIS80Hz) (-) Motor performance (tTIS80Hz, tTIS20Hz) (-) Effective connectivity (striatum → frontal cortex) (+) Side effects (N/C)
Vassiliadis *et al.* (2024) [32]	119	Healthy young/ older adults and patients with TBI	tTIS	Sham/HF control	N/A	Safety profile (N/C) Sensation magnitude (N/C) Blinding efficiency (N/C) Dropout rate (N/C)
Wang *et al.* (2024) [33]	29/30/29	Healthy adults	TIS	Sham	Simple reaction time task One-increment task	Reaction time (SRT) (+) Reaction time (one-increment) (+) (70 Hz & Sham) Mood and cognition (N/C) Neuronal damage (NSE) (N/C) EEG epileptic activity (N/C) Side effects (N/C)

Table 2. Continued.

Study	N (EG/CG)	Participants	Interven-tion	Comparison	Task	Outcome
Yang *et al.* (2024) [34]	12	Patients with mild PD	tTIS	Sham	N/A	MDS-UPDRS-III total (+) Bradykinesia (+) Tremor (+) Rigidity (N/C) Axial symptoms (N/C) Side effects (N/C) Blinding efficacy (N/C)
Zheng *et al.* (2024) [35]	20/20	Healthy young male adults	TIS	Sham	Vertical jump tests (CMJ, SJ, CJ), Y-Balance test	CMJ height (+) SJ height (+) CJ first 15 s height (+) Dynamic postural stability (N/C) Side effects (N/C) Blinding efficacy (N/C)
Zhu *et al.* (2024) [36]	32	Healthy adults	tTIS	HD-tDCS	N/A	dFC variability (CV) (+) Mean dFC strength (+) Side effects (N/C)
Wang *et al.* (2025) [37]	26	Healthy adults	TIS	Sham	N/A	Ipsilateral MEP amplitude (after 20 Hz TI) (+) Contralateral MEP amplitude (N/C) RMT (N/C) Side effects (N/C) Blinding efficacy (N/C)
Zhu *et al.* (2025) [38]	40	Healthy adults	TI	HD-tDCS	N/A	ReHo (+) Dynamic ReHo (N/C) fALFFs (+) Dynamic fALFFs (N/C) Side effects (N/C) Blinding efficacy (N/C)
Zheng *et al.* (2025) [39]	25	Healthy adults	TI	Sham	*n*-Back task (1-back, 3-back)	Working memory performance (d′) (+) Reaction time (N/C) Task-evoked BOLD activation (+) Functional connectivity (MFG-IPL) (+) Side effects (N/C) Blinding efficacy (N/C)

N/C: no change, RRTT: random reaction time task, SRTT: serial reaction time task, HF: high frequency, OSA: obstructive sleep apnea, GCLR: grid cell-like representation, EC: entorhinal complex, HC–EC: hippocampal–entorhinal complex, MDD: major depressive disorder, ET: essential tremor, PD: Parkinson's disease, CMJ: countermovement Jump, SJ: squat Jump, CJ: continuous Jump, CV: coefficient of variation, MEP: motor evoked potential, RMT: resting motor threshold, fALFFS: fractional amplitude of low-frequency fluctuations.

(MDD), PD, ET, and traumatic brain injury.

3) Stimulation protocol

Stimulation protocols were analyzed to understand the methodological characteristics of TIS. In the included studies, the primary motor cortex (M1) was the most frequently targeted area. Deep brain regions, such as the striatum and hippocampus, were also targeted [24]. Most studies applied a stimulation intensity of 2.0 mA, whereas some applied intensities of 4.0 mA or more [21]. Wang *et al.* [33] applied a notably high intensity of 15.0 mA (zero-to-peak, ZTP) to M1, representing the highest among the reviewed studies. The core of the TIS protocol involves two high-frequency carriers (F) and their ΔF. Most previous studies applied approximately 2,000 Hz as the carrier frequency. However, other carrier frequencies were also used, such as 5,000 Hz by Missey *et al.* [23], 1,000 Hz by Demchenko *et al.* [27] and Thiele *et al.* [30], and 900 Hz by Liu *et al*. [28]. Wang *et al.* [33] applied a much higher carrier frequency of 20,000 Hz. ΔF is a key factor that determines the neuromodulatory effect of TIS. The most commonly used ΔF was 20 Hz. However,

Table 3. Stimulation protocol.

Study	Site	type	Intensity (mA)	F (Hz)	ΔF (Hz)
Ma *et al.* (2022) [17]	Left primary motor cortex (M1)	TIS	2.0	2,000 and 2,020 2,000 and 2,070	20 / 70
Piao *et al.* (2022) [18]	Left primary motor cortex (M1)	TI-tACS	2.0	2,000 and 2,020 2,000 and 2,070	20 / 70
Von Conta *et al.* (2022) [19]	Parieto-occipital region (posterior cortex, alpha band targeting)	tTIS	1.0	(1,000 − IAF/2) and (1,000 + IAF/2)	IAF
Zhang *et al.* (2022) [20]	Right middle frontal gyrus (MFG), Inferior parietal lobule (IPL)	TIS	2.0	2,000 and 2,006	6
Zhu *et al.* (2022) [21]	Left primary motor cortex (M1)	TI	2.0	2,000 and 2,020	20
Iszak *et al.* (2023) [22]	Peripheral muscles	TI	4.0	2,000 and 2,005–2,010	5
	Retina		4.0	2,000 and 2,010	10
	Occipital cortex		4.0	2,000 and 2,010	10
Missey *et al.* (2023) [23]	Hypoglossal nerve (peripheral)	bTI	4.6–7.9	5,000 and 6,000	50
Violante *et al.* (2023) [24]	Hippocampus	TIS	2.0 (1:1), 1.0/3.0 (1:3)	2,000 and 2,005	5
Wessel *et al.* (2023) [25]	Striatum (putamen)	tTIS	2.0	2,000 and 2,100	100 (burst) 5 (burst train)
Beanato *et al.* (2024) [26]	Right hippocampal-entorhinal complex (HC-EC)	tTIS	2.0	2,000 and 2,100	100 (burst) 5 (burst train)
Demchenko *et al.* (2024) [27]	Subgenual anterior cingulate cortex (sgACC)	tTIS	2.0	1,000 and 1,130	130
Liu *et al.* (2024) [28]	Substantia nigra (midbrain)	TIS	2.0	900 and 1,030	130
Modak *et al.* (2024) [29]	Left caudate	TIS	2.0	2,000 and 2,020	20
Thiele *et al.* (2024) [30]	Parieto-occipital cortex	tTIS	2.0	1,000 and 1,000 + IAF	IAF
Vassiliadis *et al.* (2024) [31]	Bilateral striatum	tTIS	2.0	1,960 and 2,040 1,990 and 2,010	80 / 20
Vassiliadis *et al.* (2024) [32]	Striatum, hippocampus	tTIS	0.5–2.0	2,000 and 2,100 1,990 and 2,010 1,960 and 2,040	20/80 / iTBS/ cTBS
Wang *et al.* (2024) [33]	Left primary motor cortex (M1)	TIS	15.0 (ZTP)	20,000 and 20,020 20,000 and 20,070	20/70
Yang *et al.* (2024) [34]	Right globus pallidus internus (GPi)	tTIS	2.0/2.5	1,300 and 1,430	130
Zheng *et al.* (2024) [35]	Lower limb motor control area (Leg area of M1)	TIS	2.0	2,000 and 2,020	20
Zhu *et al.* (2024) [36]	Left first dorsal interosseous area	tTIS	2.0	2,000 and 2,020	20
Wang *et al.* (2025) [37]	Left primary motor cortex (M1)	TIS	2.0	2,000 and 2,010 / 2,020 / 2,040	10 / 20 / 40
Zhu *et al.* (2025) [38]	Left primary motor cortex (M1)	TI	2.0	2,000 and 2,020	20
Zheng *et al.* (2025) [39]	Right MFG and IPL (frontoparietal network)	TIS	2.0	2,000 and 2,006	6

IAF: individual alpha frequency, MFG: middle frontal gyrus, IPL: inferior parietal lobule

various *ΔF* values were also applied, such as 5, 80, and 130 Hz. Von Conta *et al.* [19] and Thiele *et al.* [30] aimed to achieve precise stimulation by using individual alpha frequency as the *ΔF*.

4) Task characteristics during stimulation

The literature included in this review assessed the behavioral and physiological effects of TIS during or immediately after stimulation using various tasks. These tasks were broadly categorized into three domains: motor performance, cognitive function, and sensory/perceptual processing.

In the reviewed studies, motor performance was the most frequently evaluated, with a focus on understanding the impact of TIS on motor function. Reaction time and motor efficiency were evaluated using the random reaction

time task, serial reaction time task [17], simple reaction time task, and one-increment task [33]. The sequential finger-tapping task [25] and force-tracking motor learning with reinforcement [31] were employed to evaluate motor performance accuracy and motor learning. Furthermore, muscle strength and functional motor abilities were evaluated using the vertical jump test, Y-balance test [35], and Purdue Pegboard test [18]. Various cognitive tasks were employed to investigate the effect of TIS on cognitive function. The N-back task was used to evaluate the maintenance and manipulation abilities of working memory. The face-name paired associative task was employed to assess episodic memory formation and the VR spatial navigation task to measure spatial memory and navigation abilities. Moreover, a Shepard mental rotation task was used to assess visuospatial cognition by measuring the mental manipulation and processing speed of visual images. The visual change detection task was used to measure selective attention and visual change detection ability. In addition, the apnea–hypopnea index was used as the primary outcome measure to assess the severity of OSA.

The utilization of these diverse tasks highlights the potential of TIS to have a broad impact on the different functional domains of human behavior, including motor function, cognitive function, and clinical symptoms, and contributes to the quantification of the effects of TIS according to the specific hypothesis of each study.

3.3. Quantitative Synthesis: Reported Effects of M1 Stimulation on Reaction Time

To quantitatively examine the effects of temporal interference stimulation (TIS) applied over the primary motor cortex (M1) on reaction time (RT), we extracted and summarized the statistical outcomes reported in individual studies. Table 4 presents the effect sizes, test statistics, and significance levels for RT outcomes.

Across the included studies, significant reductions in RT were observed in Ma *et al.* (2022) under the RRTT (70 Hz vs Sham) and SRTT (20 Hz vs Sham) tasks, and in Wang *et al.* (2024) during the one-increment task (70 Hz vs Sham). In addition, Piao *et al.* (2022) reported a trend toward faster RT in the SPM2 condition, and Wang *et al.* (2024) observed a borderline effect in the simple RT task, suggesting that 70 Hz stimulation may prevent RT slowing seen in the sham group.

Overall, these findings indicate that M1-targeted TIS demonstrates promising but variable effects on RT, with significant improvements in certain task conditions and frequencies (particularly 20 Hz and 70 Hz), while other conditions show only trend-level or inconsistent outcomes.

4. Discussion

TIS has garnered increasing attention for its potential to noninvasively target deep brain structures more effectively than conventional NIBS techniques. This systematic review assessed the clinical efficacy and safety of TIS, focusing exclusively on studies involving direct application to human participants.

This review indicates that TIS can contribute to the improvement of various neurological and psychiatric symptoms. Notably, positive outcomes have been reported for improvements in motor and cognitive functions, working memory, and symptoms in diseases such as obstructive sleep apnea (OSA), major depressive disorder (MDD), Parkinson's disease (PD), and essential tremor (ET). For example, a recent study by Missey *et al.* (2023) demonstrated that TIS targeting the hypoglossal nerve successfully reduced apnea events in OSA patients [23]. These findings indicate that TIS may provide diverse clinical benefits through targeted modulation of neural

Table 4. Stimulation protocol.

Study	Task	Condition	N	Effect size/Stat	P value	Reported Effect
Ma et al. (2022)	RRTT	70 Hz vs Sham	21	$d = 0.716$ t = -2.953	$p = 0.019$	Significant RT reduction
	SRTT	20 Hz vs Sham	29	$d = 0.625$ $t = -2.577$	$p = 0.041$	Significant RT reduction
Piao et al. (2022)	A-CalCAP – SPM2	Active vs Sham	19 vs 19	$F = 2.886$	$p = 0.098$	Trend toward faster RT
Wang et al. (2024)	SRT	70 Hz vs Sham	29 vs 28	$\eta^2 = 0.063$ $F(1,55) = 3.729$	$p = 0.059$	Borderline faster RT(prevented sham slowing)
	One-increment task	70 Hz vs Sham	29 vs 28	$d = 0.338$ $t(28) = 2.091$	$p = 0.046$	Significant RT reduction

A-CalCAP – SPM2: Abbreviated version of the California Computerized Assessment Package - Serial Pattern Matching 2, RRTT: random reaction time task, SRT: simple reaction time, SRTT: serial reaction time task.

circuits.

In the reviewed studies, the most frequently targeted area was the primary motor cortex (M1). This suggests active efforts to explore the effect of TIS on motor function modulation. TIS demonstrated the ability to noninvasively target and effectively modulate deep brain structures, such as the hippocampus and basal ganglia. Furthermore, TIS has shown potential applications involving the hypoglossal nerve, peripheral musculature, and the retina, indicating its utility may extend beyond the central nervous system. These results align with the theoretical mechanism indicating that TIS reduces the impact on superficial tissues through the interference of high-frequency carrier currents while generating low-frequency electric fields corresponding to the ΔF in deep areas to modulate neural activity. This mechanism is theoretically applicable to human neurophysiology.

Most of the reviewed studies applied a stimulation intensity of 2.0 mA. This may reflect a common choice considering the balance between safety and efficacy. However, some studies have applied higher or variable intensities. Wang *et al.* [33] applied 15.0 mA (ZTP), whereas Missey *et al.* [23] applied 4.6–7.9 mA, suggesting an intensity adjustment in accordance with the characteristics of the target area or research purpose. The stimulation intensity directly affects the strength of the electric field delivered to the target tissue. Thus, an accurate intensity setting is essential for the effective manifestation of TIS outcomes.

A wide range of ΔF values (5–130 Hz) was applied across studies. The most commonly used ΔF was 20 Hz, which aligned with the beta band associated with motor cortex modulation [16]. The method employed by von Conta *et al.* [19] and Thiele *et al*. [30], which involves the use of individual alpha frequency as ΔF, which highlights the potential of TIS for personalized treatment based on an individual's unique brainwave characteristics. The studies included in this review showed considerable heterogeneity in stimulation protocols, reflecting the early stage of TIS research (Heterogeneity of Stimulation Protocols and a Roadmap for Future Research). (1) Theoretical Background of Parameter Choices: The carrier frequency (e.g., 2 kHz vs. 20 kHz) affects tissue penetration, while the ΔF (e.g., 20 Hz vs. 130 Hz) influences the entrainment of endogenous rhythms in the target neural network. (2) Roadmap for Future Research: Future studies should conduct systematic parameter-sweeping studies to standardize protocols for specific clinical targets.

Most studies reported TIS to be safe, with minimal adverse effects primarily limited to skin irritation. Majority of the side effects were limited to skin irritation, and there were no serious neurological or psychological adverse effects. This is a key advantage because unlike DBS, TIS does not carry the risk of infection or hemorrhage associated with invasive procedures.

Despite providing insights into the clinical applicability of this approach by including only human-targeted TIS studies, this review has several limitations. First, most of the TIS studies conducted to date focused on healthy adults, with relatively few studies targeting populations with specific diseases. More clinical studies focusing on diverse patient populations are warranted to establish the clinical efficacy of TIS. Second, substantial heterogeneity in stimulation protocols hindered direct comparison and reduced generalizability. Systematic exploration is necessary to establish optimal stimulation protocols for specific diseases and target areas. Third, majority of the studies evaluated the effects of a single session or short-term stimulation, and data on the long-term effects and maintenance period of TIS are insufficient. Future research should explore the long-term efficacy and maintenance period of TIS to confirm its sustained benefits.

A key limitation of this review is the absence of a systematic risk of bias assessment for individual studies. Our RoB 2 analysis (Fig. 2) revealed that some studies had a 'some concerns' level of bias, suggesting that their results should be interpreted with caution and may influence the overall conclusions of this review.

Despite these limitations, this systematic review is important as it included human-targeted TIS studies, demonstrating the clinical relevance of this novel noninvasive DBS technology and providing fundamental information necessary for future research and treatment development.

5. Conclusion

This study comprehensively analyzed studies that directly applied TIS to humans to explore the clinical applicability of this novel technology and provide evidence of its efficacy and safety. This study showed that TIS is a promising neuromodulation technology capable of noninvasively and precisely stimulating deep brain structures in humans. TIS has also been shown to positively impact motor and cognitive functions as well as alleviate symptoms in various neurological disorders. Furthermore, it holds promise as a novel alternative capable of addressing the limitations of existing neuromodulation technologies.

Acknowledgements

This work was supported by grants from the National Research Foundation of Korea (NRF) funded by the Korean government (MSIT) (No. 2022R1C1C101012712 & RS-2024-00356694), the "Regional Innovation System & Education (RISE)" through the Gwangju RISE Center, funded by the Ministry of Education (MOE) and the Gwangju Metropolitan Government, Republic of Korea (2025-RISE-05-011).

References

[1] Y. Liu, Q. Zhang, H. Zhang, Y. Xiang, and H. Wang, Front. Hum. Neurosci. **19**, 1574721 (2025).
[2] N. A. Mekhail, J. Cheng, S. Narouze, L. Kapural, M. N. Mekhail, and T. Deer, Pain Pract. **10**, 103 (2010).
[3] J. S. Perlmutter and J. W. Mink, Annu. Rev. Neurosci. **29**, 229 (2006).
[4] B. F. Saway, C. Palmer, C. Hughes, M. Triano, R. E. Suresh, J. Gilmore, M. George, S. A. Kautz, and N. C. Rowland, Neurotherapeutics **21**, e00337 (2024).
[5] M. Z. Zarzycki and I. Domitrz, Acta Neuropsychiatr. **32**, 57 (2020).
[6] X. Liu, F. Qiu, L. Hou, and X. Wang, Front. Behav. Neurosci. **15**, 820017 (2022).
[7] H. Cao, L. Shang, D. Hu, J. Huang, Y. Wang, M. Li, and J. Liu, Neural Regen. Res. **21**, 491 (2026).
[8] Z. Zibly, S. Averbuch, and M. Deogaonker, Neurol. India **68**, S316 (2020).
[9] R. Chen, L. Huang, R. Wang, J. Fei, H. Wang, and J. Wang, Brain Sci. **14**, 354 (2024).
[10] A. El Baroudi, F. Razafimahery, and L. R. Rakotomanana, Eur. J. Comput. Mech. **18**, 55 (2009).
[11] N. Grossman, D. Bono, N. Dedic, S. B. Kodandaramaiah, A. Rudenko, H. J. Suk, and E. S. Boyden, Cell **169**, 1029 (2017).
[12] Z. Zhu and L. Yin, Front. Hum. Neurosci. **17**, 1266753 (2023).
[13] X. Liu, S. Qi, L. Hou, Y. Liu, and X. Wang, Mol. Neurobiol. **61**, 3314 (2024).
[14] S. Rampersad, B. Roig-Solvas, M. Yarossi, P. P. Kulkarni, E. Santarnecchi, A. D. Dorval, and D. H. Brooks, NeuroImage **202**, 116124 (2019).
[15] A. Pogosyan, L. D. Gaynor, A. Eusebio, and P. Brown, Curr. Biol. **19**, 1637 (2009).
[16] M. Arbesman, J. Scheer, and D. Lieberman, Occup. Ther. Pract. **13**, 18 (2008).
[17] R. Ma, X. Xia, W. Zhang, Z. Lu, Q. Wu, J. Cui, and X. Zhang, Front. Neurosci. **15**, 800436 (2022).
[18] Y. Piao, R. Ma, Y. Weng, C. Fan, X. Xia, W. Zhang, and X. Zhang, Brain Sci. **12**, 1194 (2022).
[19] J. von Conta, F. H. Kasten, K. Schellhorn, B. Ćurčić-Blake, A. Aleman, and C. S. Herrmann, Cortex **154**, 299 (2022).
[20] Y. Zhang, Z. Zhou, J. Zhou, Z. Qian, J. Lü, L. Li, and Y. Liu, Front. Hum. Neurosci. **16**, 918470 (2022).
[21] Z. Zhu, Y. Xiong, Y. Chen, Y. Jiang, Z. Qian, J. Lu, and J. Zhuang, Neural Plast. **2022**, 7605046 (2022).
[22] K. Iszak, S. M. Gronemann, S. Meyer, A. Hunold, J. Zschüntzsch, M. Bähr, and A. Antal, Biomedicines **11**, 1813 (2023).
[23] F. Missey, M. S. Ejneby, I. Ngom, M. J. Donahue, J. Trajlinek, E. Acerbo, and A. Williamson, Bioelectron. Med. **9**, 18 (2023).
[24] I. R. Violante, K. Alania, A. M. Cassarà, E. Neufeld, E. Acerbo, R. Carron, and N. Grossman, Nat. Neurosci. **26**, 1994 (2023).
[25] M. J. Wessel, E. Beanato, T. Popa, F. Windel, P. Vassiliadis, P. Menoud, and F. C. Hummel, Nat. Neurosci. **26**, 2005 (2023).
[26] E. Beanato, H. J. Moon, F. Windel, P. Vassiliadis, M. J. Wessel, T. Popa, and F. C. Hummel, Sci. Adv. **10**, eado4103 (2024).
[27] I. Demchenko, S. Rampersad, A. Datta, A. Horn, N. W. Churchill, S. H. Kennedy, and V. Bhat, Front. Neurosci. **18**, 1390250 (2024).
[28] R. Liu, G. Zhu, Z. Wu, Y. Gan, J. Zhang, J. Liu, and L. Wang, NeuroImage **291**, 120581 (2024).
[29] P. Modak, J. Fine, B. Colon, E. Need, H. Cheng, L. Hulvershorn, and J. W. Brown, Brain Stimul. **17**, 867 (2024).
[30] C. Thiele, K. S. Rufener, S. Repplinger, T. Zaehle, and P. Ruhnau, Psychophysiology **61**, e14651 (2024).
[31] P. Vassiliadis, E. Beanato, T. Popa, F. Windel, T. Morishita, E. Neufeld, and F. C. Hummel, Nat. Hum. Behav. **8**, 1581 (2024).
[32] P. Vassiliadis, E. Stiennon, F. Windel, M. J. Wessel, E. Beanato, and F. C. Hummel, J. Neural Eng. **21**, 024001 (2024).
[33] Y. Wang, G. Q. Zeng, M. Wang, M. Zhang, C. Chang, Q. Liu, and X. Zhang, Front. Hum. Neurosci. **18**, 1484593 (2024).
[34] C. Yang, Y. Xu, X. Feng, B. Wang, Y. Du, K. Wang, and Y. Liu, Mov. Disord. **40**, 1061 (2024).
[35] S. Zheng, T. Fu, J. Yan, C. Zhu, L. Li, Z. Qian, and Y. Liu, J. NeuroEng. Rehabil. **21**, 38 (2024).
[36] Z. Zhu, D. Tang, L. Qin, Z. Qian, J. Zhuang, and Y. Liu, Front. Hum. Neurosci. **18**, 1453638 (2024).
[37] Y. Wang, C. Zhu, J. Zhou, T. Fu, J. Yan, B. Wang, and Y. Liu, Front. Hum. Neurosci. **19**, 1524485 (2025).
[38] Z. Zhu, L. Qin, D. Tang, Z. Qian, J. Zhuang, and Y. Liu, Brain Sci. **15**, 317 (2025).
[39] S. Zheng, Y. Zhang, K. Huang, J. Zhuang, J. Lü, and Y. Liu, Hum. Brain Mapp. **46**, e70160 (2025).