Human Brain Mapping

WILEY

RESEARCH ARTICLE OPEN ACCESS

Temporal Interference Stimulation Boosts Working Memory Performance in the Frontoparietal Network

Suwang Zheng[1,2] | Yufeng Zhang[1,2] | Kun Huang[3] | Jie Zhuang[3] | Jiaojiao Lü[1,2] | Yu Liu[1,2]

[1]Key Laboratory of Exercise and Health Sciences of Ministry of Education, Shanghai University of Sport, Shanghai, China | [2]School of Exercise and Health, Shanghai University of Sport, Shanghai, China | [3]School of Psychology, Shanghai University of Sport, Shanghai, China

Correspondence: Jiaojiao Lü (ljj27@163.com) | Jie Zhuang (jie.zhuang@sus.edu.cn)

Received: 12 September 2024 | **Revised:** 16 January 2025 | **Accepted:** 31 January 2025

Funding: This work was supported by National Natural Science Foundation of China (Grants 11932013 and 12302418), Humanities and Social Science Fund of Ministry of Education of China (Grant 21YJA190013) and the Sports Science & Technology Project of Shanghai (Grant 24J013).

Keywords: fMRI | frontoparietal network | functional connectivity | temporal interference stimulation | working memory

ABSTRACT

Temporal interference (TI) stimulation is a novel neuromodulation technique that overcomes the depth limitations of traditional transcranial electrical stimulation while avoiding the invasiveness of deep brain stimulation. Our previous behavioral research has demonstrated the effects of multi-target TI stimulation in enhancing working memory (WM) performance, however, the neural mechanisms of this special form of envelope modulation remain unclear. To address this issue, here we designed this randomized, double-blind, crossover study, which consisted of a task-based functional magnetic resonance imaging (fMRI) experiment, to explore how offline TI stimulation modulated brain activity and behavioral performance in healthy adults. We conducted a 2×2 within-subjects design with two factors: stimulation (TI vs. Sham) and time (pre vs. post). Participants received two stimulation protocols in a random order: TI (beat frequency: 6 Hz, targeting middle frontal gyrus [MFG] and inferior parietal lobule [IPL]) and sham stimulation. Neuroimaging data of a WM task with different cognitive loads were acquisited immediately before and after stimulation. We found TI stimulation significantly improved d' in the high-demand WM task. Whole-brain analysis showed the significant time-by-stimulation interactions in two main clusters in IPL and precuneus with lower activation after TI stimulation. The generalized psychophysiological interaction (gPPI) analysis revealed a significant interaction in task-modulated connectivity between MFG and IPL, with improvement observed after TI stimulation. Notably, this increasing functional connectivity induced by TI stimulation was positively correlated with better behavioral performance. Overall, our findings show specific effects of TI stimulation on brain activation and functional connectivity in the frontoparietal network and may contribute to provide new perspectives for future neuromodulation applications.

1 | Introduction

Temporal interference (TI) stimulation, as a novel neuromodulation technique, overcomes the limitations of traditional noninvasive brain stimulation (NIBS) and deep brain stimulation (DBS), and thus provide new opportunities for neuroscience research and clinical practice (Grossman et al. 2018). TI electrical fields require at least two pairs of electrodes placed on the head with each pair delivering a high-frequency alternating current. The small difference of frequency between each alternating current was considered as the key to neuromodulation, allowing us to modulate deep brain regions in a noninvasive and focal manner without affecting the overlying areas (Grossman et al. 2017; Polanía et al. 2018). Recent

The first two authors contributed equally to this article and share first authorship.

studies indicated this low-frequency envelope could modulate neural activities and improve human cognitive performance (Esmaeilpour et al. 2021; Vassiliadis, Beanato et al. 2024; Violante et al. 2023; Wessel et al. 2023).

Based on the hypothesis of network dynamics and neural interactions, it is necessary to explore the feasibility and mechanisms of diverse stimulation protocols to meet the needs of complex clinical applications (Bassett and Sporns 2017; Dagan et al. 2018; Violante et al. 2017). For instance, transcranial alternating current stimulation (tACS), designed to target the prefrontal and temporal cortices, has shown potential benefits in maintaining or improving cognition in older adults (Reinhart and Nguyen 2019). Considering the critical role of deep brain areas in many neural circuits (such as motor control and memory), the advent of TI opened up possibilities for exploring more diverse protocols to enhance human performance or alleviate pathological symptoms (Beliaeva et al. 2021; Guo et al. 2023; Hummel and Wessel 2024; Zhu and Yin 2023). However, current TI protocols predominantly focus on single-target stimulation, such as M1 (Zheng et al. 2024; Zhu et al. 2022), hippocampus (Violante et al. 2023), and striatum (Vassiliadis, Beanato et al. 2024; Wessel et al. 2023). The effectiveness of multi-target TI stimulation remains to be explored. Given the current scarcity of studies on simultaneous stimulation of multiple deep targets, the unclear causal relationship between deep brain oscillations and behavior, and the lack of consistent results across studies, the frontal–parietal network (FPN) was chosen as the focus of this study to preliminarily investigate the modulation effects of multi-target TI stimulation. Our previous study has verified the feasibility and safety of frontoparietal TI stimulation on working memory (WM) performance in healthy adults (Zhang et al. 2022). This multi-target TI stimulation demonstrated similar modulation effects to tACS behaviorally without neuroimaging evidence, thus making it difficult to explain its positive effects on WM from a neurophysiological perspective. In this context, while it does not directly address neural oscillatory phase relationships, functional magnetic resonance imaging (fMRI) provides a powerful tool for investigating target and network engagement with its high spatial resolution (Esmaeilpour et al. 2020). It also enables the exploration of coordinated activity patterns across brain areas (Beliaeva et al. 2021). Existing studies have provided valuable evidence on brain activity induced by TI stimulation. However, findings remain diverse, with stimulation-induced changes in average brain activation showing increases (Wessel et al. 2023), decreases (Violante et al. 2023), or no change (Vassiliadis, Beanato et al. 2024) in target area, and varying correlations with behavioral performance. We hope this fMRI study could provide more valuable insights into the development of diversified stimulation protocols for future applications.

In this article, we conducted a task-based fMRI experiment to explore the effects of multi-target TI stimulation on brain activity and behavioral performance in a WM task in healthy adults. We also evaluated the possible association between these changes in behavioral performance and changes in neural activity induced by TI stimulation. We hypothesized that (1) TI stimulation would improve behavioral performance in the high-demand WM task, increase WM-related brain activation and functional connectivity compared with sham stimulation (Sham); (2) the changes in WM performance induced by TI stimulation may correlate with the changes in functional connectivity between frontal and parietal areas.

2 | Methods

2.1 | Participants

Considering that interindividual variability might affect the effectiveness of NIBS, all the participants recruited in this study were healthy adults, as they exhibited lower variability of brain structure and cognitive function.

Twenty-five participants completed this study and were included in the behavioral analysis (10 males and 15 females; age: 22.480 ± 1.358 years; education level: 16.200 ± 1.155 years), and 20 of them were included in the fMRI data analysis (8 males and 12 females; age: 22.500 ± 1.147 years; education level: 16.250 ± 0.967 years). Five participants were excluded for excessive head movement. The inclusion criteria were as follows: (1) 18–35 years old; (2) right-handed; (3) no unhealthy life habits (such as excessive smoking, alcoholism); (4) normal cognitive function with the Mini-Mental State Examination (MMSE) score > 27; (5) normal or corrected-to-normal vision. The exclusion criteria were as follows: (1) history of psychiatric or neurological disorders; (2) metal implants; (3) receiving NIBS within 1 month; (4) any personal or family history of a neurological or psychiatric disorder (see Figure 1 for participant flow diagram).

All participants attended the experiment at the same time of a day for each visit. The participants were instructed to refrain from staying up late, strenuous exercise, and drinking coffee or alcoholic beverages. None of the participants reported taking any medications during the study period. Ethical approval was granted by the Institutional Review Board of Shanghai University of Sport (102772022RT048).

2.2 | Experimental Design

In this randomized, double-blind, crossover study, all participants received two stimulation protocols in a random order separated by a 7-day washout period: (1) frontoparietal TI stimulation; (2) Sham.

Each participant had three visits. During Visit 1, the participant demographic information (gender, age, and education level) was collected and all were trained on a *n*-back task to minimize the practice effect in subsequent formal experiment. During the familiarization phase, all participants were required to achieve at least 75% accuracy. Each participant randomly received one stimulation (TI or Sham) at Visit 2, and received another stimulation protocol at the next visit. The fMRI data and behavioral data were collected before and after each intervention. The flow chart for the experimental design was shown in Figure 2A. Questionnaires on blinding efficacy and side effects were completed by all participants at the end of Visits 2 and 3.

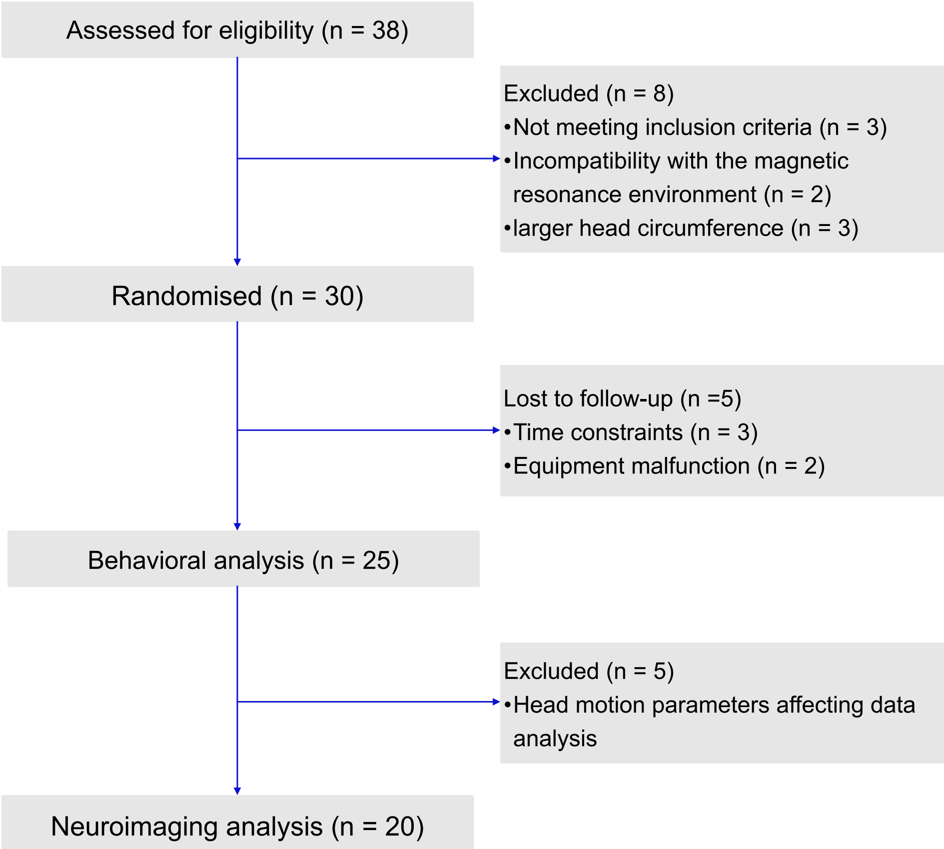

FIGURE 1 | Flow of participants through the trial.

2.3 | Stimulation Paradigm

The intervention was conducted by the Interferential Neuromodulation System (Soterix Medical, NewYork, NY). The stimulation regions-of-interest (ROIs) were the middle frontal gyrus (MFG) and inferior parietal lobule (IPL), which corresponded to F4 and P4, respectively, in the 10–20 international electroencephalography (EEG) localization system (Zhang et al. 2022; Violante et al. 2017). To achieve multi-target modulation, four channels of high frequency alternating current were used, with each pair of currents (I_1: 2 kHz, 2 mA; I_2: 2.006 kHz, resulting in a beat frequency of 6 Hz) generating a TI electric field targeting each ROI (for detailed electrode placement and electromagnetic computation data, see Figure S1). The peak-to-peak amplitude of the current was set at 2 mA. The duration of TI protocol was 20 min. The parameters of Sham protocol were identical to those of TI protocol, except that the current was only delivered at the first 15 s and the last 15 s of the whole stimulation session. The impedance was kept below 15 kΩ during stimulation.

2.4 | Working Memory Task

The working-memory experimental paradigm (i.e., *n*-back task) was presented in an alternating block design, using letters as stimuli. The paradigm consisted of a rest block (30 s) and two tasks at different difficulty levels (1-back and 3-back; see Figure 2C). Each scanning session included two functional runs, with a 2-min interval between them. During each run, there were four task blocks (1-back, 3-back, 1-back, 3-back) with 25 trials in a 1-back block and 40 trials in a 3-back block (Figure 2B). In each trial, a stimulus was presented on the screen for 600 ms, followed by a fixation cross for 2400 ms. Participants were asked to judge as accurately and quickly as possible whether the current stimulus was identical to the one presented *n* trials before.

The *n*-back task was implemented in MATLAB (MathWorks) using the Psychophysics Toolbox (http://psychtoolbox.org). Memory performance measures of *n*-back task included *d* prime ($d' = z(\text{Hit}) - z(\text{False alarm})$) (Haatveit et al. 2010; Williams et al. 2022) and reaction time (RT; only from correct responses).

2.5 | MRI Data Acquisition

MRI data were collected in a Siemens 3 T MAGNETOM Prisma scanner (Siemens, Erlangen, Germany). Structural images were acquired using T1-weighted 3D magnetization-prepared rapid gradient-echo imaging sequence (MP-RAGE) with the following parameters: repetition time (TR) = 2300 ms, echo time (TE) = 2.98 ms, inverse time (TI) = 900 ms, slices = 176, flip angle = 9°, field of view (FOV) = $256 \times 256\ \text{mm}^2$, voxel size = $1 \times 1 \times 1\ \text{mm}^3$. Functional images were acquired using a gradient echo-echo planar imaging (GE-EPI): TR = 2100 ms, TE = 27 ms, flip angle = 80°, FOV = $210 \times 210\ \text{mm}^2$, matrix

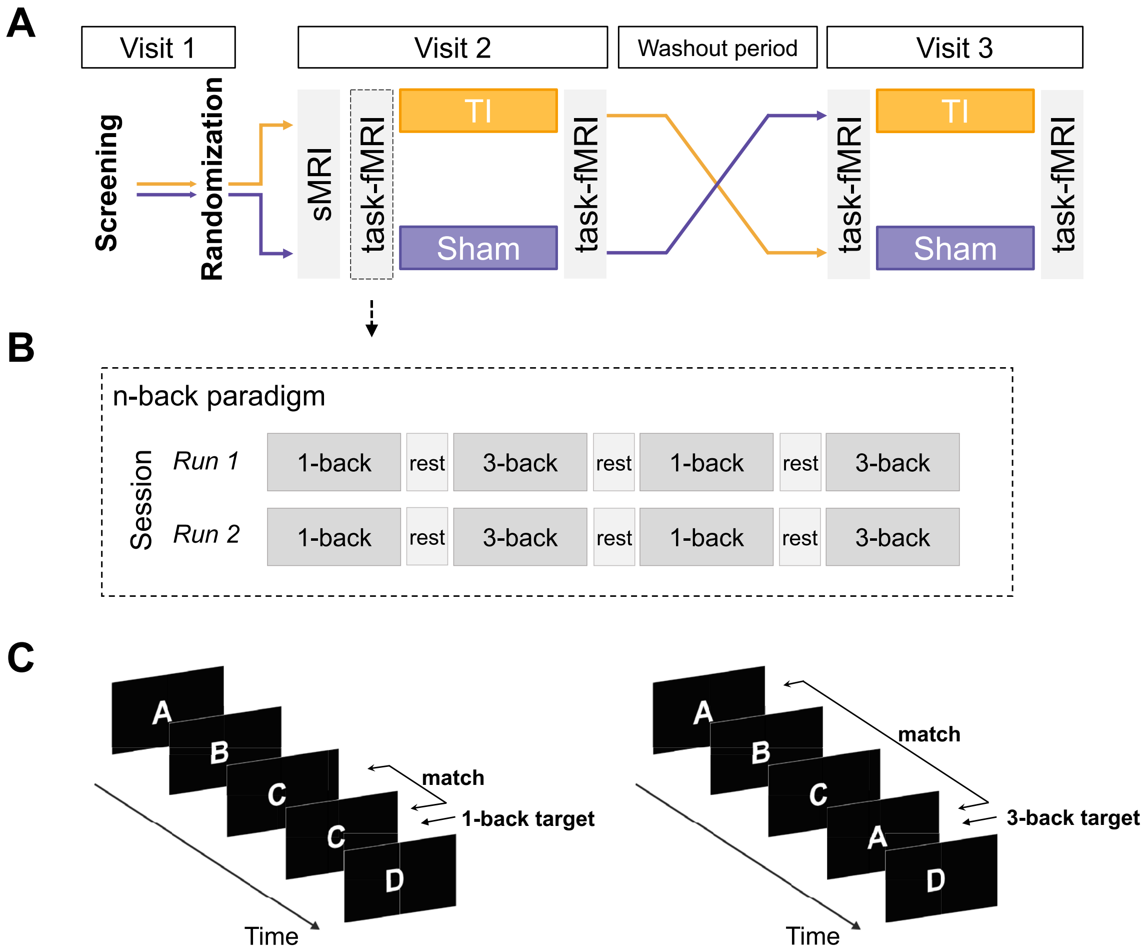

FIGURE 2 | Study design and working memory task paradigm. (A) Study design. In this randomized, double-blind, crossover study, participants had three visits and received two stimulation protocols in a random order separated by 7-day washout period. Before and immediately after intervention, task-fMRI data was acquired. (B) N-back task paradigm in fMRI. The working-memory experimental paradigm consisted of a rest block and two tasks with increasing difficulty (1-back and 3-back). During each MRI session, participants performed two runs of *n*-back task and each run consisted of two tasks that alternated twice. (C) Illustration of the 1-back (left) and 3-back (right) task. The *n*-back task required participants to determine whether the currently presented stimulus matched the one presented *n* steps earlier.

size = 64 × 64 pixels, voxel size = $3 \times 3 \times 3\,mm^3$, slice thickness = 3 mm, gap = 0 mm, 40 slices, interleaved acquisition.

2.6 | fMRI Data Analysis

2.6.1 | Preprocessing

All images were preprocessed in SPM 12 (Welcome Trust Center for Neuroimaging, University College London, https://www.fil.ion.ucl.ac.uk/spm/). The first four volumes of each functional run were discarded to allow for steady-state equilibrium. Slice-timing correction was performed to correct timing differences in slice acquisition. All functional images were aligned to the first image in each run to eliminate motion artifacts. After re-alignment, T1 weighed structural images were co-registered with the mean realigned functional images. Segmentation of the T1 weighted structural image was performed, then normalized to the Montreal Neurological Institute (MNI) template. The same transformation parameters were then applied to all functional images. Finally, the normalized images of 3 × 3 × 3 mm were smoothed using a Gaussian kernel with a full-width half-maximum of 6 × 6 × 6 mm. Five participants were excluded from further analyses because of unacceptable head movements (translation > 3 mm or rotation > 3°).

2.6.2 | Univariate fMRI Analyses

FMRI data was analyzed in SPM12 using the general linear model (GLM). Regressors were convolved with the canonical hemodynamic response function. The design matrix in each run of this study included three independent events: 1-back (low WM load), 3-back (high WM load), errors, and six motion parameters (three rotations, three translations). In the first-level analysis, single-subject statistical parametric maps for high load-specific WM-related activity were calculated using corresponding contrasts: 3-back versus 1-back. For the second-level group analysis, a two-way repeated-measures ANOVA was performed to investigate the interaction effect between stimulation type (TI/Sham) and time (pre/post). The significant threshold was set at voxel-level ($p < 0.001$, uncorrected) and cluster-level ($p < 0.05$, family-wise error [FWE] corrected).

2.6.3 | Task-Based Functional Connectivity Analysis

To examine the functional connectivity modulated by task conditions, we used a generalized psychophysiological interaction (gPPI) analysis. This whole-brain seed-to-voxel analysis was conducted based on SPM12 and gPPI toolbox (http://www.nitrc.org/projects/gppi) (McLaren et al. 2012). Considering the stimulation target region, we selected two WM-related ROIs from a meta-analysis of verbal WM fMRI study (Emch et al. 2019): MFG ($x=46$, $y=34$, $z=18$) and IPL ($x=40$, $y=-46$, $z=48$). The deconvolved time series from ROIs were extracted to create the physiological variable. The PPI-GLM included the physiological variable (time series of ROI), the psychological variable (task condition), the PPI term, and motion parameters. For each model, the PPI interaction terms were created by the physiological term and the psychological term. After calculating fMRI contrasts (3-back > 1-back) in the first-level analysis, a two-way repeated-measures ANOVA was performed to investigate the interaction effect between stimulation type (TI/Sham) and time (pre/post). The significant threshold was set at voxel-level ($p < 0.001$, uncorrected) and cluster-level ($p < 0.05$, FWE corrected).

2.7 | Statistical Analysis

Based on the previous behavioral studies (Biel et al. 2022; Polanía et al. 2012; Violante et al. 2017; Zhang et al. 2022), we anticipated an effect size of 0.30. Using this effect size estimate, a priori power analysis with a significance level of $\alpha=0.05$ and a power of $1-\beta=0.80$ determined that a minimum of 24 participants would be required.

All behavioral data was analyzed using SPSS 29.0 statistic software (SPSS Inc., Chicago, IL, USA). The Shapiro–Wilk normality test was performed to test for normality distribution. If these data were not normally distributed, logarithmic transformation was applied for normal transformation. A 2×2 repeated measures ANOVA was performed to examine the effects of TI stimulation on WM performance. Post hoc comparisons were conducted using the Bonferroni method. For fMRI data, Marsbar toolbox (http://sourceforge.net/projects/marsbar) was used to extracted mean beta values of each significant cluster. Post hoc analyses, with Bonferroni's correction, were then conducted to determine the direction of stimulation-induced brain activity changes. Neuroimaging results visualization was carried out using BrainNet Viewer (https://www.nitrc.org/projects/bnv/) (Xia et al. 2013) and MRIcroGL (https://www.nitrc.org/projects/mricrogl/). Based on the hypothesis of a positive correlation between neural activity and behavioral performance changes, Pearson's correlation test (one-tail) was used to assess the relationship between the changes in brain activation induced by stimulation and corresponding behavioral changes, as well as changes in functional connectivity strength induced by stimulation and behavioral performance changes. For the blinding efficacy, we used $R\times C$ chi-square test or Fisher's exact test to determine whether the distribution of participants' guesses of stimulation types differed between stimulation conditions (i.e., TI or Sham). Side effects were analyzed by Wilcoxon signed-rank test. Unless otherwise noted, data were presented as mean ± standard deviation (SD) in the text. Significant level (α) was set at 0.05 in all behavioral analyses.

3 | Results

3.1 | Behavioral Performance

To behaviorally evaluate WM performance, we used a n-back task at different difficulty levels (1-back and 3-back). The effect of TI stimulation on WM performance (d' and RT) with different cognitive load was assessed (Figure 3). For d prime, a two-way repeated measures ANOVA showed a significant interaction effect between stimulation conditions and time in the 3-back task ($F=6.518$, $p=0.017$, $\eta_p^2=0.214$). In further post hoc analysis, we found a significant post-intervention improvement of d'in the 3-back task in TI condition ($p<0.001$, Cohen's $d=-0.902$, 95% CI of difference: −0.931 to −0.346), but no significant improvement in Sham condition ($p=0.076$, Cohen's $d=-0.371$, 95% CI of difference: −0.395 to 0.021). The post hoc analysis also showed a significant difference between TI condition and Sham condition after intervention ($p=0.028$, Cohen's $d=0.468$, 95% CI of difference: 0.039–0.624), but no significant difference between these two conditions before intervention ($p=0.305$, Cohen's $d=-0.210$, 95% CI of difference: −0.356 to 0.116). In the 1-back task, no significant main effects or interactions were observed (all $ps > 0.493$). For RT, there were significant time main effects in the 1-back task ($F=46.194$, $p<0.001$, $\eta_p^2=0.658$) and the 3-back task ($F=49.383$, $p<0.001$, $\eta_p^2=0.673$), but no stimulation main effect and interaction effect (all $ps > 0.485$).

3.2 | Modulation of WM Task-Evoked Activity

An important goal of this study was to investigate the changes of neural activity in WM induced by TI stimulation. Clusters obtained from a whole-brain activation analysis with a significant interaction effect were illustrated in Table 1 and Figure 4. The significant interaction was revealed in the IPL (BA 39, 40), angular gyrus (ANG; BA 39), superior parietal gyrus (SPG; BA 7), middle occipital gyrus (MOG, BA 19), precuneus (PCUN; BA 5, 7), and paracentral lobule (PCL).

To further understand the effects of stimulation on the target regions, we extracted the beta value of each of these significant clusters. Post hoc tests revealed that, compared to pre-intervention, activation values were significantly lower after stimulation in TI condition for the PCUN cluster (pre: 0.663 ± 1.350 vs. post: −0.911 ± 1.742, $p=0.026$, Cohen's $d=0.612$, adjusted 95% CI of difference: 0.174–2.973) and IPL cluster (pre: 1.810 ± 1.278 vs. post: 0.467 ± 1.213, $p=0.001$, Cohen's $d=0.906$, adjusted 95% CI of difference: 0.536–2.150). In Sham condition, no significant difference in PCUN between pre- and post- intervention (pre: −0.034 ± 1.368 vs. post: 0.963 ± 1.736, $p=0.125$, Cohen's $d=-0.442$, adjusted 95% CI of difference: −2.225 to 0.230) but an increasing trend could be found in IPL (pre: 0.814 ± 1.336 vs. post: 1.789 ± 1.167, $p=0.033$, Cohen's $d=-0.589$, adjusted 95% CI of difference:

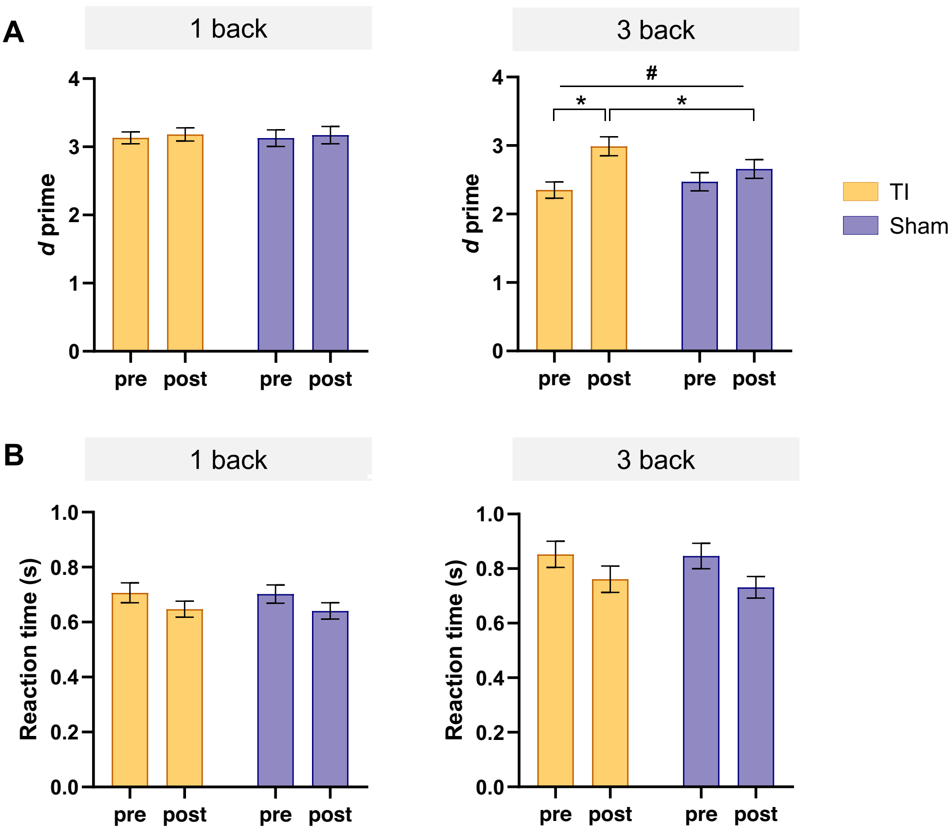

FIGURE 3 | Working memory behavioral performance (mean ± SEM). (A) d' for 1-back and 3-back. There was a significant interaction effect in the 3-back. Post hoc analysis showed a significant post-intervention improvement in TI condition, compared to Sham condition. Additionally, there was a significant difference between the TI condition and the Sham condition after intervention compared to before intervention. (B) Reaction time for 1-back and 3-back. This variable did not follow a normal distribution and was log-transformed for statistical analysis. The figures show raw values. There was no significant interaction effect for RT. Error bars represent SEM; $^{\#}$significant interaction effect ($p<0.05$); *significant difference at post hoc analysis ($p<0.05$, Bonferroni's corrected).

TABLE 1 | Whole brain activation analysis results.

				MNI coordinates (mm)			
Cluster regions	**BA**	**Size (voxels)**	**Max *Z***	***x***	***y***	***z***	***F***
(L) IPL, ANG, SPG, MOG	39, 40, 7, 19	43	3.9367	−30	−64	44	18.9502
(L/R) PCUN, (L)PCL	7, 5	31	3.4838	6	−40	53	14.7981

Note: Voxel level, $p<0.001$ uncorrected; cluster level, $p<0.05$, FWE corrected.
Abbreviations: ANG, angular gyrus; IPL, inferior parietal, but supramarginal and angular gyri; MOG, middle occipital gyrus; PCL, paracentral lobule; PCUN, precuneus; SPG, superior parietal gyrus.

−1.875 to −0.074). Figure 4 illustrates the changes in BOLD signal activation induced by stimulation.

The Pearson correlation analysis revealed no significant correlation between changes in IPL activation and the corresponding behavioral changes ($r=-0.085$, $p=0.301$), as well as between changes in PCUN activation and the corresponding behavioral changes ($r=-0.046$, $p=0.389$).

3.3 | Task-Modulated Functional Connectivity

We next assessed whether frontoparietal TI stimulation modulated functional connectivity in the brain in a gPPI analysis (Table 2). There was a significant interaction of functional connectivity between the MFG-seed and IPL (BA 40; $x=-39$, $y=-40$, $z=41$; Figure 5A). In contrast, no modulation of functional connectivity was observed for the IPL-seed. Our post hoc results demonstrated that, task-modulated functional connectivity between MFG and IPL increased after TI stimulation (pre: −0.474 ± 0.891 vs. post: 0.420 ± 0.385, $p<0.001$, Cohen's $d=-0.943$, 95% CI of difference: −1.338 to −0.450), but decreased after Sham (pre: −0.057 ± 0.678 vs. post: −0.608 ± 0.889, $p=0.024$, Cohen's $d=0.550$, 95% CI of difference: 0.082–1.020). Figure 5B illustrates the changes in functional connectivity induced by stimulation.

We further examined the relationship between functional connectivity strength and behavioral performance induced by

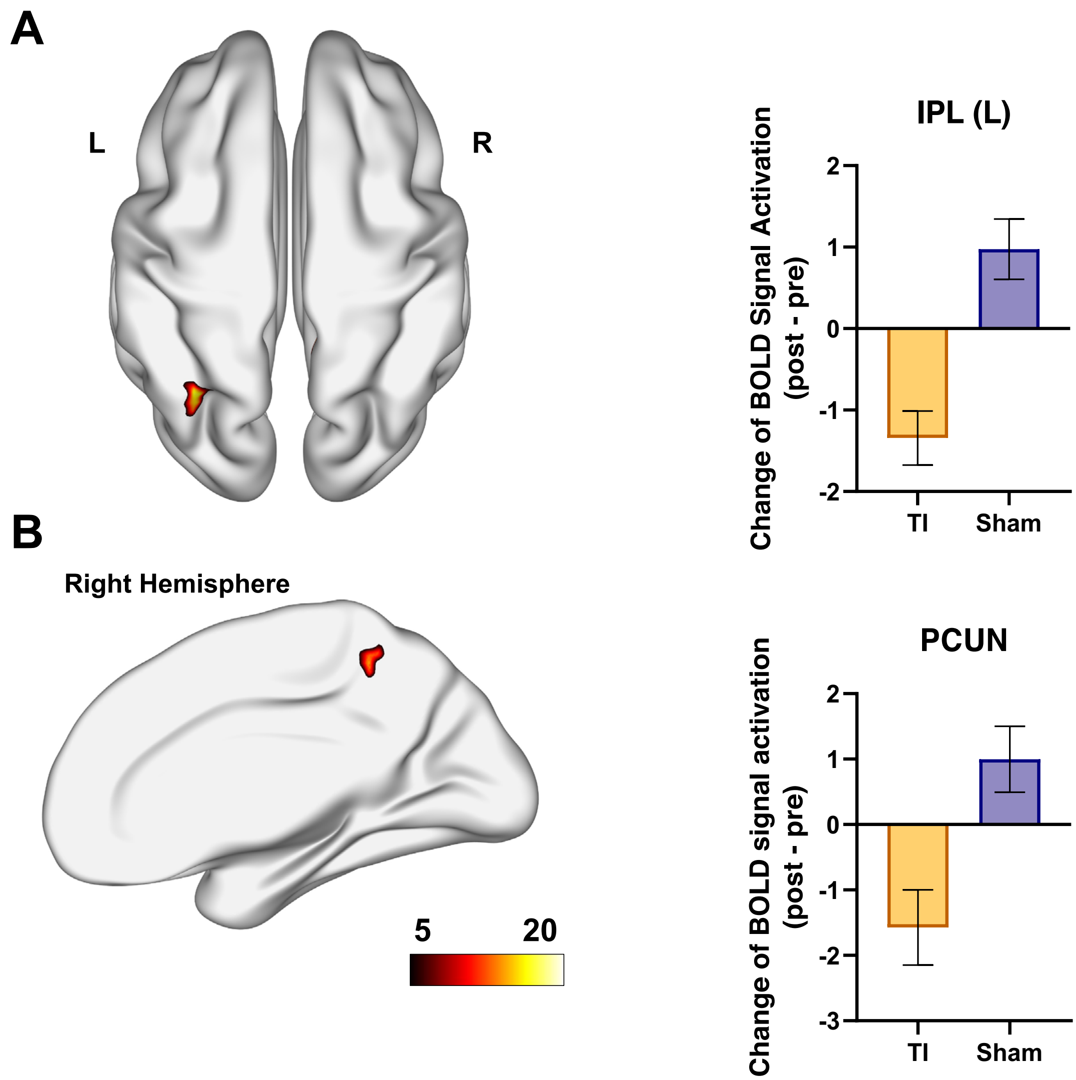

FIGURE 4 | Significant interaction effect during WM task (mean ± SEM). Whole brain activation analysis showed the significant cluster included (A) the inferior parietal lobule, angular gyrus, superior parietal gyrus, middle occipital gyrus, and (B) precuneus, and paracentral lobule. The right column showed the extracted activation value from each cluster to determine the direction of modulation changes induced by intervention. Changes in activation values showed different trends in the two conditions: Decreased in the TI condition but increased in the Sham condition. Error bars represent SEM. Voxel level, $p < 0.001$ uncorrected; cluster level, $p < 0.05$, FWE corrected.

TABLE 2 | Functional connectivity results.

				MNI coordinates (mm)			
Cluster regions	**BA**	**Size (voxels)**	**Max *Z***	***x***	***y***	***z***	***F***
Seed: MFG ($x = 46, y = 34, z = 18$)							
(L) IPL	40	28	4.1311	−39	−40	41	20.9505
Seed: IPL ($x = 40, y = -46, z = 48$)							
No significant cluster							

Note: Voxel level, $p < 0.001$ uncorrected; cluster level, $p < 0.05$, FWE corrected.
Abbreviations: IPL, inferior parietal, but supramarginal and angular gyri; MFG, mddle frontal gyrus.

stimulation. A Pearson correlation analysis indicated a significant positive correlation between better WM performance (d') and increasing functional connectivity strength between the MFG and IPL ($r = 0.284$, $p = 0.038$, one-tail, Figure 5C).

3.4 | Blinding Efficacy and Side Effects

Fisher's exact tests revealed no significant difference in the proportion of guesses for each intervention type between the two

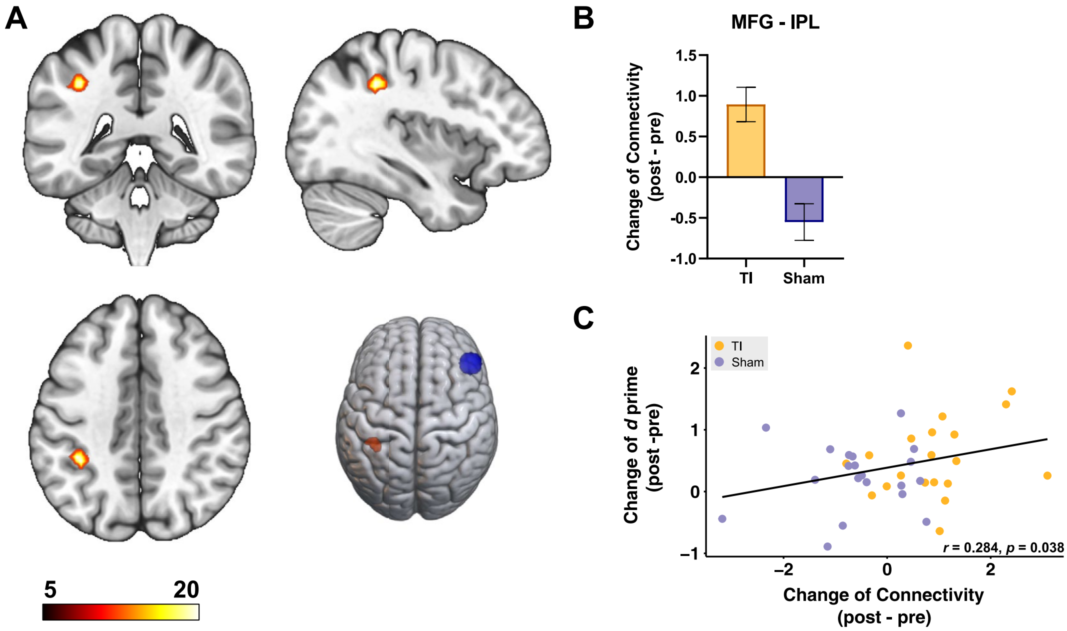

FIGURE 5 | Functional connectivity results and its correlation with behavioral performance (mean ± SEM). (A) There was a significant interaction effect on functional connectivity between frontal lobe and parietal lobe. (B) Task-modulated functional connectivity between MFG and IPL increased after TI condition but decreased after Sham. (C) Significant correlation was observed between the improved connectivity between IPL and MFG and the enhanced WM behavioral performance (d') induced by stimulation. Error bars represent SEM. Voxel level, $p < 0.001$ uncorrected; cluster level, $p < 0.05$, FWE corrected.

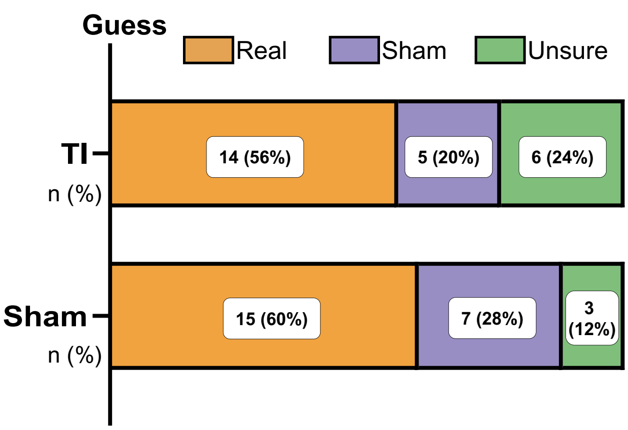

FIGURE 6 | Blinding efficacy of TI and sham stimulation.

stimulation conditions ($p = 0.544$, Figure 6), indicating successful blinding. Participants primarily experienced a tingling sensation and fatigue during the experiment, with the severity of all side effects being moderate or less. There was no significant difference in side effects between stimulation conditions (all *ps* > 0.157, Table 3).

4 | Discussion

This randomized, double-blind, crossover study examined the effect of TI stimulation targeted FPN on WM performance and its neurophysiological bases. Specifically, we found that TI stimulation could enhance WM performance with high memory load, accompanied by significant neurophysiological changes. Neuroimaging analysis demonstrated that TI stimulation induced activation decreases in WM-related brain areas (such as IPL and precuneus) and the functional connectivity increase between IPL and MFG. Importantly, the changes of frontoparietal functional connectivity were significantly correlated with that of WM performance. Additionally, our stimulation protocol was well-tolerated, with no serious side effects occurring, consistent with the previous studies (Piao et al. 2022; Vassiliadis, Stiennon et al. 2024; Zhang et al. 2022).

4.1 | WM Performance

Our behavioral findings suggested TI stimulation, implemented through beat frequency modulation, could enhance the WM performance of healthy adults in a load-dependence manner. TI stimulation improved the d' metric in high WM load tasks (i.e., 3-back task), while performance on the 1-back task was unaffected. The 1-back task showed a ceiling effect, thereby providing insufficient discriminative power for performance changes in normal cognitive function population. Compared to the 1-back task, the 3-back task imposes greater cognitive demands on healthy individuals, with the frontoparietal regions more actively engaged in cognitive processing (Dima et al. 2013; Heinzel et al. 2017; Manelis and Reder 2014; Satake et al. 2024). Consequently, it is more responsive to modulation by externally applied electrical stimulation targeting these regions, as evidenced by findings from studies combining NIBS with fMRI and EEG analyses (Polanía et al. 2012; Ratcliffe et al. 2022; Violante et al. 2017).

Our results were similar to those of tACS studies (Jaušovec and Jaušovec 2014; Violante et al. 2017). The low-frequency envelope may enhance WM by entraining theta oscillations in FPN,

TABLE 3 | Reported side effects of TI stimulation and sham stimulation.

	None	Mild	Moderate	Severe	*Z*	*p*
Tingling						
TI	10 (40%)	13 (52%)	2 (8%)	0 (0%)	−1.387	0.166
Sham	5 (20%)	18 (72%)	2 (8%)	0 (0%)		
Itching						
TI	22 (88%)	3 (12%)	0 (0%)	0 (0%)	−1.414	0.157
Sham	20 (80%)	3 (12%)	2 (8%)	0 (0%)		
Burning						
TI	21 (84%)	4 (16%)	0 (0%)	0 (0%)	−1.342	0.180
Sham	24 (96%)	1 (4%)	0 (0%)	0 (0%)		
Pain						
TI	18 (72%)	7 (28%)	0 (0%)	0 (0%)	−0.447	0.655
Sham	19 (76%)	6 (24%)	0 (0%)	0 (0%)		
Skin redness						
TI	24 (96%)	1 (4%)	0 (0%)	0 (0%)	−1.000	0.317
Sham	25 (100%)	0 (0%)	0 (0%)	0 (0%)		
Fatigue						
TI	12 (48%)	12 (48%)	1 (4%)	0 (0%)	< 0.001	> 0.999
Sham	13 (52%)	10 (40%)	2 (8%)	0 (0%)		
Phosphene						
TI	23 (92%)	2 (8%)	0 (0%)	0 (0%)	−0.577	0.564
Sham	24 (96%)	1 (4%)	0 (0%)	0 (0%)		
Inattention						
TI	13 (52%)	11 (44%)	1 (4%)	0 (0%)	−1.265	0.206
Sham	9 (36%)	15 (60%)	1 (4%)	0 (0%)		
Mood swings						
TI	21 (84%)	4 (16%)	0 (0%)	0 (0%)	−0.577	0.564
Sham	22 (88%)	3 (12%)	0 (0%)	0 (0%)		

serving as a gating mechanism essential for the integration and modulation of WM processes (Raghavachari et al. 2001; Sauseng et al. 2010; Sauseng and Klimesch 2008). Additionally, spike-timing-dependent plasticity (STDP) could explain the observed offline effects, as oscillatory electric fields can induce lasting changes in synaptic connectivity, supporting the transient maintenance of WM items (Schwab et al. 2021; Elyamany et al. 2021; Huang and Wei 2021; Vogeti et al. 2022).

4.2 | Brain Activation

Our neuroimaging experiment aimed to investigate the effects of TI stimulation on neural activity evoked by WM tasks. We demonstrated that the TI stimulation with a theta-band frequency difference reduced the task-related BOLD activity in the inferior parietal lobe (BA 39, 40), and precuneus (BA 7). The study on hippocampus-targeted TI stimulation reported the similar decrease trend of BOLD signal evoked by episodic memory (Violante et al. 2023).

The observed reduction in activity in non-target, WM-related regions may be explained by the neural efficiency hypothesis, which reflects the redistribution or reorganization of BOLD signals (Kelly and Garavan 2005; Neubauer and Fink 2009). These processes involve shifting reliance on task-specific or process-specific brain areas. The left IPL plays a role in facilitating information storage and retrieval during high-demand WM tasks (Albouy et al. 2018; Baldo and Dronkers 2006; Jaušovec and Jaušovec 2014; Jonides et al. 1998). This reduction likely indicates an efficiency-driven adaptation, characterized by decreased reliance on the IPL during WM tasks. Such efficiency might arise from a reduction in the number of neurons actively engaged in the cognitive process while maintaining sufficient capacity for information manipulation and retention (Constantinidis and Klingberg 2016). However, further neurophysiological studies are needed to confirm this hypothesis in the cognitive domain. In this context, participants may shift from controlled, effortful processing to more automated strategies, similar to the effects observed in WM training (Constantinidis and Klingberg 2016; Hosseini et al. 2016; Jung and Haier 2007; Olesen et al. 2004; Sayala et al. 2006). These automated strategies, which consume less cognitive energy, are likely underpinned by plasticity changes in the neural systems. It is worth noting that our crossover design minimized and balanced practice effects across stimulation conditions. However, we cannot entirely rule out the possibility that TI stimulation mediated cognitive learning processes over repeated task trials.

Additionally, no correlation was found between brain activation changes and behavioral performance, suggesting that these changes may not directly correspond to behavioral outcomes in a linear manner. This highlights the complex and potentially nonlinear—and even non-monotonic—relationship between stimulation-induced neural activation changes and cognitive performance. While reduced neural effort reflects increased efficiency, this relationship has its limitations, as further reductions in activation do not necessarily translate to better functional outcomes. Overall, our findings suggest that TI stimulation may enhance cognitive efficiency, enabling better behavioral performance with reduced cognitive resource or energy consumption.

4.3 | Functional Connectivity

Functional connectivity is a commonly used measure to investigate functional brain networks, representing the coordinated communication between distinct brain regions (Fingelkurts et al. 2005; Ghobadi-Azbari et al. 2021). FPN is essential for supporting WM functions (Hampson et al. 2006). In this study, the increased functional connectivity between MFG and IPL after TI stimulation has been observed. This finding aligns with results from previous tACS studies (Biel et al. 2022; Albouy et al. 2017; Grover et al. 2021; Polanía et al. 2012; Violante et al. 2017). More importantly, the strengthened functional connectivity correlated significantly with improvements in high-load WM performance, supporting the hypothesis that the dynamics of FPN may underlie the improvements in high-load WM performance induced by TI stimulation.

Prior research has suggested that frontoparietal functional connectivity exhibits WM load dependency (Heinzel et al. 2017). From a functional perspective, IPL is primarily involved in information storage processes (Baldo and Dronkers 2006), while MFG plays a key role in task control, employing top-down mechanisms to sustain, monitor, update, and manipulate task-relevant information (Edin et al. 2009). Enhanced long-distance communication between MFG and IPL may facilitate the adaptive top-down control, enabling individuals to better meet external task demands. This could be attributed to oscillatory synchronization, potentially driven by shifts in the balance between excitatory and inhibitory transmission (Esmaeilpour et al. 2021; Roux and Uhlhaas 2014). Several studies emphasize that TI stimulation operates through subthreshold modulation, with electric fields and currents biasing synaptic transmission by polarizing axonal terminals (Howell and McIntyre 2021; Mirzakhalili et al. 2020). Specific synaptic states, such as strengthened connections between neurons or activity-dependent increases in axonal myelination, may underlie the observed changes in functional connectivity (Constantinidis and Klingberg 2016; Gibson et al. 2014). Moreover, while the observed connectivity changes suggest improved coordination between brain regions, fMRI data cannot capture the temporal dynamics or causal relationships underlying these effects. Further research is warranted to explore the temporal sequence of brain responses during TI stimulation and memory processing, providing deeper insights into the mechanisms of network reorganization and their influence on cognitive performance.

4.4 | The Role of Precuneus

The changes of BOLD activity were also observed in precuneus. The role of precuneus in central executive network (CEN) and default mode network (DMN) could help us understand its neural changes during WM induced by TI stimulation (Li et al. 2022; Yaple et al. 2019). From one perspective, the paracingulate network, a subnetwork of CEN defined by Dadario and Sughrue (2023), located at entirely precuneus and was considered as a task-positive network for the active maintenance and manipulation of information in WM (Dadario and Sughrue 2023). An *n*-back MEG study explored the temporal dynamics of the precuneus, revealing its role as a crucial bridge between low-level and high-level information processing (Costers et al. 2020). From another perspective, DMN, known as a task-negative network, is effectively downregulated during increased cognitive load. This downregulation has been linked to improved neural processing efficiency in cognitive tasks. The precuneus and left IPL, recognized as nodes of the DMN, may, therefore, contribute to the observed effects in this study through its role in task-negative network modulation. Moreover, the dynamic coupling between the DMN and the FPN has been shown to drive WM performance (Murphy et al. 2020; Yuan et al. 2021). Changes in functional connectivity between these two distinct networks may underlie the observed improvements in behavioral performance, although this hypothesis requires further investigation. One possible explanation is the selective opening or closing of synaptic channels between subnetworks of the DMN and FPN, which may drive transitions in activity patterns between them during cognitive tasks (Piccoli et al. 2015).

4.5 | Limitations

This investigation has some limitations. First, with the aim to preliminarily understand the neurophysiological effects of TI stimulation, we designed one control condition, but did not compare TI with tACS or high-frequency alternating current stimulation. These control groups would further elucidate the mechanisms between different forms of electrical currents (Mirzakhalili et al. 2020). Second, for the generalizability and applicability of the study results, we selected fixed parameter settings. However, individualized stimulation parameters (frequency, electrode placement, current ratio, etc.) might achieve better modulation effects considering the differences in individual anatomical structures and endogenous neural oscillation frequencies (Von Conta et al. 2021). Moreover, the unknown correspondence between brain oscillation and BOLD signal limits our further understanding of TI stimulation, which primarily uses exogenous oscillations as a modulation method.

5 | Conclusion

This study replicated the observation that multi-target TI stimulation targeted FPN improved WM performance, and provided the neurophysiological evidence of TI stimulation modulating brain activity and connectivity pattern. Our results demonstrated the TI stimulation significant induced changes of brain activation on the left parietal lobe and precuneus and the functional connectivity across FPN. We also highlight the link between the enhanced connectivity and the improved performance. Future research could leverage the advantages of TI stimulation in deep stimulation to develop diverse modulation protocols targeting specific nodes within neural circuits.

Acknowledgments

We thank Xiangming Li for assisting with programming the experimental task. This work was supported by the National Natural Science Foundation of China (Grants 11932013 and 12302418), the Humanities and Social Sciences Fund of the Ministry of Education (Grant 21YJA190013), and the Sports Science & Technology Project of Shanghai (Grant 24J013).

Ethics Statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Shanghai University of Sport (102772022RT048).

Consent

The patients/participants provided their written informed consent to participate in this study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Albouy, P., S. Baillet, and R. J. Zatorre. 2018. "Driving Working Memory With Frequency-Tuned Noninvasive Brain Stimulation." *Annals of the New York Academy of Sciences* 1423, no. 1: 126–137. https://doi.org/10.1111/nyas.13664.

Albouy, P., A. Weiss, S. Baillet, and R. J. Zatorre. 2017. "Selective Entrainment of Theta Oscillations in the Dorsal Stream Causally Enhances Auditory Working Memory Performance." *Neuron* 94, no. 1: 193–206. https://doi.org/10.1016/j.neuron.2017.03.015.

Baldo, J. V., and N. F. Dronkers. 2006. "The Role of Inferior Parietal and Inferior Frontal Cortex in Working Memory." *Neuropsychology* 20, no. 5: 529–538. https://doi.org/10.1037/0894-4105.20.5.529.

Bassett, D. S., and O. Sporns. 2017. "Network Neuroscience." *Nature Neuroscience* 20, no. 3: 353–364. https://doi.org/10.1038/nn.4502.

Beliaeva, V., I. Savvateev, V. Zerbi, and R. Polania. 2021. "Toward Integrative Approaches to Study the Causal Role of Neural Oscillations via Transcranial Electrical Stimulation." *Nature Communications* 12, no. 1: 2243. https://doi.org/10.1038/s41467-021-22468-7.

Biel, A. L., E. Sterner, L. Röll, and P. Sauseng. 2022. "Modulating Verbal Working Memory With Fronto-Parietal Transcranial Electric Stimulation at Theta Frequency: Does It Work?" *European Journal of Neuroscience* 55, no. 2: 405–425. https://doi.org/10.1111/ejn.15563.

Constantinidis, C., and T. Klingberg. 2016. "The Neuroscience of Working Memory Capacity and Training." *Nature Reviews Neuroscience* 17, no. 7: 438–449. https://doi.org/10.1038/nrn.2016.43.

Costers, L., J. Van Schependom, J. Laton, et al. 2020. "Spatiotemporal and Spectral Dynamics of Multi-Item Working Memory as Revealed by the n-Back Task Using MEG." *Human Brain Mapping* 41, no. 9: 2431–2446. https://doi.org/10.1002/hbm.24955.

Dadario, N. B., and M. E. Sughrue. 2023. "The Functional Role of the Precuneus." *Brain* 146, no. 9: 3598–3607. https://doi.org/10.1093/brain/awad181.

Dagan, M., T. Herman, R. Harrison, et al. 2018. "Multitarget Transcranial Direct Current Stimulation for Freezing of Gait in Parkinson's Disease." *Movement Disorders* 33, no. 4: 642–646. https://doi.org/10.1002/mds.27300.

Dima, D., J. Jogia, and S. Frangou. 2013. "Dynamic Causal Modeling of Load-Dependent Modulation of Effective Connectivity Within the Verbal Working Memory Network." *Human Brain Mapping* 35, no. 7: 3025–3035. https://doi.org/10.1002/hbm.22382.

Edin, F., T. Klingberg, P. Johansson, F. McNab, J. Tegnér, and A. Compte. 2009. "Mechanism for Top-Down Control of Working Memory Capacity." *Proceedings of the National Academy of Sciences of the United States of America* 106, no. 16: 6802–6807. https://doi.org/10.1073/pnas.0901894106.

Elyamany, O., G. Leicht, C. S. Herrmann, and C. Mulert. 2021. "Transcranial Alternating Current Stimulation (tACS): From Basic Mechanisms Towards First Applications in Psychiatry." *European Archives of Psychiatry and Clinical Neuroscience* 271, no. 1: 135–156. https://doi.org/10.1007/s00406-020-01209-9.

Emch, M., C. C. von Bastian, and K. Koch. 2019. "Neural Correlates of Verbal Working Memory: An fMRI Meta-Analysis." *Frontiers in Human Neuroscience* 13: 180. https://doi.org/10.3389/fnhum.2019.00180.

Esmaeilpour, Z., G. Kronberg, D. Reato, L. C. Parra, and M. Bikson. 2021. "Temporal Interference Stimulation Targets Deep Brain Regions by Modulating Neural Oscillations." *Brain Stimulation* 14, no. 1: 55–65. https://doi.org/10.1016/j.brs.2020.11.007.

Esmaeilpour, Z., A. D. Shereen, P. Ghobadi-Azbari, et al. 2020. "Methodology for tDCS Integration With fMRI." *Human Brain Mapping* 41, no. 7: 1950–1967. https://doi.org/10.1002/hbm.24908.

Fingelkurts, A. A., A. A. Fingelkurts, and S. Kähkönen. 2005. "Functional Connectivity in the Brain—Is It an Elusive Concept?" *Neuroscience & Biobehavioral Reviews* 28, no. 8: 827–836. https://doi.org/10.1016/j.neubiorev.2004.10.009.

Ghobadi-Azbari, P., A. Jamil, F. Yavari, et al. 2021. "fMRI and Transcranial Electrical Stimulation (tES): A Systematic Review of Parameter Space and Outcomes." *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 107: 110149. https://doi.org/10.1016/j.pnpbp.2020.110149.

Gibson, E. M., D. Purger, C. W. Mount, et al. 2014. "Neuronal Activity Promotes Oligodendrogenesis and Adaptive Myelination in the Mammalian Brain." *Science* 344, no. 6183: 1252304. https://doi.org/10.1126/science.1252304.

Grossman, N., D. Bono, N. Dedic, et al. 2017. "Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields." *Cell* 169, no. 6: 1029–1041. https://doi.org/10.1016/j.cell.2017.05.024.

Grossman, N., M. S. Okun, and E. S. Boyden. 2018. "Translating Temporal Interference Brain Stimulation to Treat Neurological and Psychiatric Conditions." *JAMA Neurology* 75, no. 11: 1307. https://doi.org/10.1001/jamaneurol.2018.2760.

Grover, S., J. A. Nguyen, and R. M. G. Reinhart. 2021. "Synchronizing Brain Rhythms to Improve Cognition." *Annual Review of Medicine* 72, no. 1: 29–43. https://doi.org/10.1146/annurev-med-060619-022857.

Guo, W., Y. He, W. Zhang, et al. 2023. "A Novel Non-invasive Brain Stimulation Technique: 'Temporally Interfering Electrical Stimulation'." *Frontiers in Neuroscience* 17: 1092539. https://doi.org/10.3389/fnins.2023.1092539.

Haatveit, B. C., K. Sundet, K. Hugdahl, T. Ueland, I. Melle, and O. A. Andreassen. 2010. "The Validity of d Prime as a Working Memory Index: Results From the "Bergen n -Back Task"." *Journal of Clinical and Experimental Neuropsychology* 32, no. 8: 871–880. https://doi.org/10.1080/13803391003596421.

Hampson, M., N. R. Driesen, P. Skudlarski, J. C. Gore, and R. T. Constable. 2006. "Brain Connectivity Related to Working Memory Performance." *Journal of Neuroscience* 26, no. 51: 13338–13343. https://doi.org/10.1523/JNEUROSCI.3408-06.2006.

Heinzel, S., R. C. Lorenz, Q.-L. Duong, M. A. Rapp, and L. Deserno. 2017. "Prefrontal-Parietal Effective Connectivity During Working Memory in Older Adults." *Neurobiology of Aging* 57: 18–27. https://doi.org/10.1016/j.neurobiolaging.2017.05.005.

Hosseini, S. H., M. Pritchard-Berman, N. Sosa, A. Ceja, and S. R. Kesler. 2016. "Task-Based Neurofeedback Training: A Novel Approach Toward Training Executive Functions." *NeuroImage* 134: 153–159. https://doi.org/10.1016/j.neuroimage.2016.03.035.

Howell, B., and C. C. McIntyre. 2021. "Feasibility of Interferential and Pulsed Transcranial Electrical Stimulation for Neuromodulation at the Human Scale." *Neuromodulation: Journal of the International Neuromodulation Society* 24, no. 5: 843–853. https://doi.org/10.1111/ner.13137.

Huang, Q.-S., and H. Wei. 2021. "A Computational Model of Working Memory Based on Spike-Timing-Dependent Plasticity." *Frontiers in Computational Neuroscience* 15: 630999. https://doi.org/10.3389/fncom.2021.630999.

Hummel, F. C., and M. J. Wessel. 2024. "Non-invasive Deep Brain Stimulation: Interventional Targeting of Deep Brain Areas in Neurological Disorders." *Nature Reviews Neurology* 20, no. 8: 451–452. https://doi.org/10.1038/s41582-024-00990-8.

Jaušovec, N., and K. Jaušovec. 2014. "Increasing Working Memory Capacity With Theta Transcranial Alternating Current Stimulation (tACS)." *Biological Psychology* 96: 42–47. https://doi.org/10.1016/j.biopsycho.2013.11.006.

Jonides, J., E. H. Schumacher, E. E. Smith, et al. 1998. "The Role of Parietal Cortex in Verbal Working Memory." *Journal of Neuroscience* 18, no. 13: 5026–5034. https://doi.org/10.1523/JNEUROSCI.18-13-05026.1998.

Jung, R. E., and R. J. Haier. 2007. "The Parieto-Frontal Integration Theory (P-FIT) of Intelligence: Converging Neuroimaging Evidence." *Behavioral and Brain Sciences* 30, no. 2: 135–154. https://doi.org/10.1017/S0140525X07001185.

Kelly, A. M. C., and H. Garavan. 2005. "Human Functional Neuroimaging of Brain Changes Associated With Practice." *Cerebral Cortex* 15, no. 8: 1089–1102. https://doi.org/10.1093/cercor/bhi005.

Li, X., M. J. O'Sullivan, and J. B. Mattingley. 2022. "Delay Activity During Visual Working Memory: A Meta-Analysis of 30 fMRI Experiments." *NeuroImage* 255: 119204. https://doi.org/10.1016/j.neuroimage.2022.119204.

Manelis, A., and L. M. Reder. 2014. "Effective Connectivity Among the Working Memory Regions During Preparation for and During Performance of the n-Back Task." *Frontiers in Human Neuroscience* 8: 593. https://doi.org/10.3389/fnhum.2014.00593.

McLaren, D. G., M. L. Ries, G. Xu, and S. C. Johnson. 2012. "A Generalized Form of Context-Dependent Psychophysiological Interactions (gPPI): A Comparison to Standard Approaches." *NeuroImage* 61, no. 4: 1277–1286. https://doi.org/10.1016/j.neuroimage.2012.03.068.

Mirzakhalili, E., B. Barra, M. Capogrosso, and S. F. Lempka. 2020. "Biophysics of Temporal Interference Stimulation." *Cell Systems* 11, no. 6: 557–572. https://doi.org/10.1016/j.cels.2020.10.004.

Murphy, A. C., M. A. Bertolero, L. Papadopoulos, D. M. Lydon-Staley, and D. S. Bassett. 2020. "Multimodal Network Dynamics Underpinning Working Memory." *Nature Communications* 11, no. 1: 3035. https://doi.org/10.1038/s41467-020-15541-0.

Neubauer, A. C., and A. Fink. 2009. "Intelligence and Neural Efficiency." *Neuroscience and Biobehavioral Reviews* 33, no. 7: 1004–1023. https://doi.org/10.1016/j.neubiorev.2009.04.001.

Olesen, P. J., H. Westerberg, and T. Klingberg. 2004. "Increased Prefrontal and Parietal Activity After Training of Working Memory." *Nature Neuroscience* 7, no. 1: 75–79. https://doi.org/10.1038/nn1165.

Piao, Y., R. Ma, Y. Weng, et al. 2022. "Safety Evaluation of Employing Temporal Interference Transcranial Alternating Current Stimulation in Human Studies." *Brain Sciences* 12, no. 9: 1194. https://doi.org/10.3390/brainsci12091194.

Piccoli, T., G. Valente, D. E. J. Linden, et al. 2015. "The Default Mode Network and the Working Memory Network Are Not Anti-Correlated During all Phases of a Working Memory Task." *PLoS One* 10, no. 4: e0123354. https://doi.org/10.1371/journal.pone.0123354.

Polanía, R., M. A. Nitsche, C. Korman, G. Batsikadze, and W. Paulus. 2012. "The Importance of Timing in Segregated Theta Phase-Coupling for Cognitive Performance." *Current Biology* 22, no. 14: 1314–1318. https://doi.org/10.1016/j.cub.2012.05.021.

Polanía, R., M. A. Nitsche, and C. C. Ruff. 2018. "Studying and Modifying Brain Function With Non-invasive Brain Stimulation." *Nature Neuroscience* 21, no. 2: 174–187. https://doi.org/10.1038/s41593-017-0054-4.

Raghavachari, S., M. J. Kahana, D. S. Rizzuto, et al. 2001. "Gating of Human Theta Oscillations by a Working Memory Task." *Journal of Neuroscience* 21, no. 9: 3175–3183. https://doi.org/10.1523/JNEUROSCI.21-09-03175.2001.

Ratcliffe, O., K. Shapiro, and B. P. Staresina. 2022. "Fronto-Medial Theta Coordinates Posterior Maintenance of Working Memory Content." *Current Biology: CB* 32, no. 10: 2121–2129. https://doi.org/10.1016/j.cub.2022.03.045.

Reinhart, R. M. G., and J. A. Nguyen. 2019. "Working Memory Revived in Older Adults by Synchronizing Rhythmic Brain Circuits." *Nature Neuroscience* 22, no. 5: 820–827. https://doi.org/10.1038/s41593-019-0371-x.

Roux, F., and P. J. Uhlhaas. 2014. "Working Memory and Neural Oscillations: Alpha–Gamma Versus Theta–Gamma Codes for Distinct WM Information?" *Trends in Cognitive Sciences* 18, no. 1: 16–25. https://doi.org/10.1016/j.tics.2013.10.010.

Satake, T., A. Taki, K. Kasahara, D. Yoshimaru, and T. Tsurugizawa. 2024. "Comparison of Local Activation, Functional Connectivity, and Structural Connectivity in the N-Back Task." *Frontiers in Neuroscience* 18: 1337976. https://doi.org/10.3389/fnins.2024.1337976.

Sauseng, P., B. Griesmayr, R. Freunberger, and W. Klimesch. 2010. "Control Mechanisms in Working Memory: A Possible Function of EEG Theta Oscillations." *Neuroscience & Biobehavioral Reviews* 34, no. 7: 1015–1022. https://doi.org/10.1016/j.neubiorev.2009.12.006.

Sauseng, P., and W. Klimesch. 2008. "What Does Phase Information of Oscillatory Brain Activity Tell Us About Cognitive Processes?"

Neuroscience & Biobehavioral Reviews 32, no. 5: 1001–1013. https://doi.org/10.1016/j.neubiorev.2008.03.014.

Sayala, S., J. B. Sala, and S. M. Courtney. 2006. "Increased Neural Efficiency With Repeated Performance of a Working Memory Task Is Information-Type Dependent." *Cerebral Cortex* 16, no. 5: 609–617. https://doi.org/10.1093/cercor/bhj007.

Schwab, B. C., P. König, and A. K. Engel. 2021. "Spike-Timing-Dependent Plasticity Can Account for Connectivity Aftereffects of Dual-Site Transcranial Alternating Current Stimulation." *NeuroImage* 237: 118179. https://doi.org/10.1016/j.neuroimage.2021.118179.

Vassiliadis, P., E. Beanato, T. Popa, et al. 2024a. "Non-invasive Stimulation of the Human Striatum Disrupts Reinforcement Learning of Motor Skills." *Nature Human Behaviour* 8, no. 8: 1–18. https://doi.org/10.1038/s41562-024-01901-z.

Vassiliadis, P., E. Stiennon, F. Windel, M. J. Wessel, E. Beanato, and F. C. Hummel. 2024b. "Safety, Tolerability and Blinding Efficiency of Non-invasive Deep Transcranial Temporal Interference Stimulation: First Experience From More Than 250 Sessions." *Journal of Neural Engineering* 21, no. 2: 024001. https://doi.org/10.1088/1741-2552/ad2d32.

Violante, I. R., K. Alania, A. M. Cassarà, et al. 2023. "Non-invasive Temporal Interference Electrical Stimulation of the Human Hippocampus." *Nature Neuroscience* 26, no. 11: 1994–2004. https://doi.org/10.1038/s41593-023-01456-8.

Violante, I. R., L. M. Li, D. W. Carmichael, et al. 2017. "Externally Induced Frontoparietal Synchronization Modulates Network Dynamics and Enhances Working Memory Performance." *eLife* 6: e22001. https://doi.org/10.7554/eLife.22001.

Vogeti, S., C. Boetzel, and C. S. Herrmann. 2022. "Entrainment and Spike-Timing Dependent Plasticity—A Review of Proposed Mechanisms of Transcranial Alternating Current Stimulation." *Frontiers in Systems Neuroscience* 16: 827353. https://doi.org/10.3389/fnsys.2022.827353.

Von Conta, J., F. H. Kasten, B. Ćurčić-Blake, A. Aleman, A. Thielscher, and C. S. Herrmann. 2021. "Interindividual Variability of Electric Fields During Transcranial Temporal Interference Stimulation (tTIS)." *Scientific Reports* 11, no. 1: 20357. https://doi.org/10.1038/s41598-021-99749-0.

Wessel, M. J., E. Beanato, T. Popa, et al. 2023. "Noninvasive Theta-Burst Stimulation of the Human Striatum Enhances Striatal Activity and Motor Skill Learning." *Nature Neuroscience* 26: 2005–2016. https://doi.org/10.1038/s41593-023-01457-7.

Williams, J. R., M. M. Robinson, M. W. Schurgin, J. T. Wixted, and T. F. Brady. 2022. "You Cannot "Count" How Many Items People Remember in Visual Working Memory: The Importance of Signal Detection–Based Measures for Understanding Change Detection Performance." *Journal of Experimental Psychology: Human Perception and Performance* 48, no. 12: 1390–1409. https://doi.org/10.1037/xhp0001055.

Xia, M., J. Wang, and Y. He. 2013. "BrainNet Viewer: A Network Visualization Tool for Human Brain Connectomics." *PLoS One* 8, no. 7: e68910. https://doi.org/10.1371/journal.pone.0068910.

Yaple, Z. A., W. D. Stevens, and M. Arsalidou. 2019. "Meta-Analyses of the n-Back Working Memory Task: fMRI Evidence of Age-Related Changes in Prefrontal Cortex Involvement Across the Adult Lifespan." *NeuroImage* 196: 16–31. https://doi.org/10.1016/j.neuroimage.2019.03.074.

Yuan, Y., X. Pan, and R. Wang. 2021. "Biophysical Mechanism of the Interaction Between Default Mode Network and Working Memory Network." *Cognitive Neurodynamics* 15, no. 6: 1101–1124. https://doi.org/10.1007/s11571-021-09674-1.

Zhang, Y., Z. Zhou, J. Zhou, et al. 2022. "Temporal Interference Stimulation Targeting Right Frontoparietal Areas Enhances Working Memory in Healthy Individuals." *Frontiers in Human Neuroscience* 16: 918470. https://doi.org/10.3389/fnhum.2022.918470.

Zheng, S., T. Fu, J. Yan, et al. 2024. "Repetitive Temporal Interference Stimulation Improves Jump Performance but Not the Postural Stability in Young Healthy Males: A Randomized Controlled Trial." *Journal of Neuroengineering and Rehabilitation* 21, no. 1: 38. https://doi.org/10.1186/s12984-024-01336-7.

Zhu, Z., Y. Xiong, Y. Chen, et al. 2022. "Temporal Interference (TI) Stimulation Boosts Functional Connectivity in Human Motor Cortex: A Comparison Study With Transcranial Direct Current Stimulation (tDCS)." *Neural Plasticity* 2022: 7605046. https://doi.org/10.1155/2022/7605046.

Zhu, Z., and L. Yin. 2023. "A Mini-Review: Recent Advancements in Temporal Interference Stimulation in Modulating Brain Function and Behavior." *Frontiers in Human Neuroscience* 17: 1266753. https://doi.org/10.3389/fnhum.2023.1266753.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.