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Neurostimulation: exploring perceptual & cognitive enhancement

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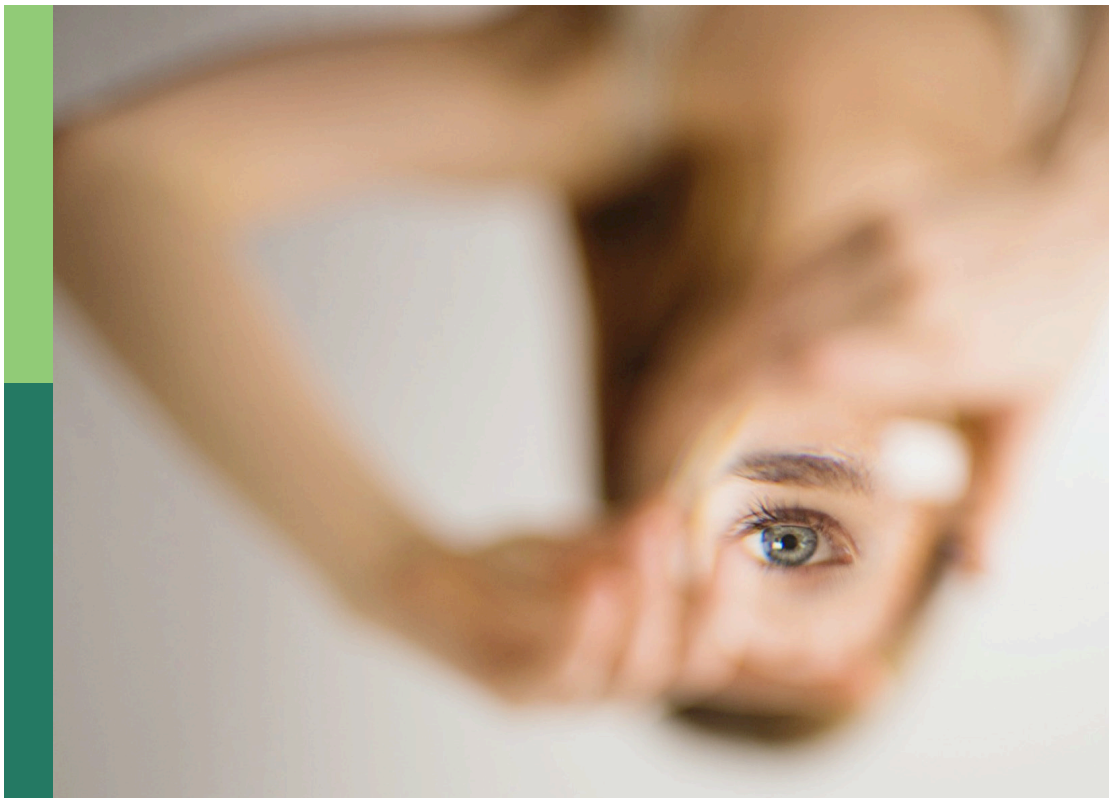

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Neurostimulation: exploring perceptual & cognitive enhancement

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Editorial: Neurostimulation: exploring perceptual & cognitive enhancement

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Editorial on the Research Topic
Neurostimulation: exploring perceptual & cognitive enhancement

Introduction

The use of electricity to artificially stimulate the nervous system dates to 15AD where electric fish were used to treat pain and headaches (Gildenberg, 2006). It wasn't until the 1960ʳs that modern neuromodulation emerged by way of deep brain, and then spinal cord, stimulation. Today, various forms of neurostimulation exist which involve stimulating peripheral sensory nerves (Toth et al., 2019; Maurer et al., 2001; Johnson and Wilson, 2018), the cortex (Toth et al., 2023; Galvin et al., 2023; Bruton et al., 2020), and the cerebellum (Lam et al., 2017), with both electric (tES) and magnetic fields (TMS). Our understanding of the mechanisms by which this stimulation affects neural communication has deepened and allowed for the controlled excitation and inhibition of cortical regions to probe and alter their function during various tasks (Castelli et al., 2025) Due to the ease with which motor performance can be evaluated, the primary motor cortex has been a popular target among neurostimulation studies, and, as such, promising results have been found regarding the efficacy of neurostimulation to influence and even augment various motor skills.

It is only more recently that neurostimulation has emerged as a promising avenue for enhancing cognitive and perceptual abilities. Transcranial electric current stimulation (tES), in particular, has garnered significant research attention given its simplicity and the fact that commercial tES devices are now readily available (Wexler, 2020). Given commercial devices can fall between regulatory gaps (clinical, consumer applications) some caution is needed especially regarding improperly applied neurostimulation (e.g., montage placement, modified devices and electric currents, contraindication screening). Although, transcranial magnetic stimulation (TMS) and transcranial pulse stimulation (TPS) have also been explored for their potential to improve attention, memory, reaction times, decision-making, and learning (Grafman and Wassermann, 1998). These techniques

are being investigated across various domains, from clinical interventions for neurological conditions (Edwards et al., 2017) to cognitive enhancement in healthy individuals (Curtin et al., 2019). This editorial synthesizes recent findings pertaining to the implications for neurostimulation to enhance perceptual and cognitive abilities.

Neurostimulation and cognition

Memory and learning are key areas where neurostimulation is being applied. A study combining computerized cognitive training (CCT) with different forms of transcranial electric stimulation (tDCS and tACS) found that stimulation effects varied based on individual factors such as age and education (Krebs et al.). Specifically, older individuals with higher education levels benefited more from tDCS, while younger individuals with less education responded better to tACS. Overall, this study highlights the importance of individualized stimulation protocols to maximize cognitive benefits. However, the findings regarding the efficacy for tES to enhance cognition in older populations is particularly interesting given it bolsters previous work (Kraft and Hampstead, 2024), as well as work using alterative neurostimulation techniques. For example, in another study (Zhang et al.) repetitive transcranial magnetic stimulation (rTMS) was examined as a potential intervention for early cognitive decline in individuals with subjective cognitive decline (SCD). Participants who received rTMS over the left dorsolateral prefrontal cortex (DLPFC) showed improvements in episodic memory, suggesting that neurostimulation may serve as an early intervention for Alzheimer's disease and related disorders. Furthermore, the study highlighted the role of long-term potentiation (LTP)-like cortical plasticity as a potential biomarker for cognitive improvement, paving the way for future research on neurostimulation in neurodegenerative conditions. Additionally, Zhang et al. evidenced LTP-like cortical plasticity behaviorally but also via TMS-EEG indices (TMS evoked potentials) and in doing so provide a more direct measure of cortical activation/reactivity following their intervention. This is in contrast to other work which tends to infer cellular mechanisms rather than direct receptor level measurement.

When considering more complex executive functions, such as problem-solving and cognitive flexibility, the effects of tES are less conclusive. A study investigating tDCS over the dorsolateral prefrontal cortex found that its efficacy in enhancing cognitive function was not as pronounced as its effects on motor learning (Toth et al.). Interestingly, the study suggested that sex differences might play a role in determining stimulation outcomes, with males showing greater benefits on simple attention tasks. This corroborates findings from a study using transcranial magnetic stimulation (TMS) to investigate how modulating activity in the right pre-supplementary motor area (RpSMA) and medial cerebellar vermis (MCV6) affected reaction times (Zhao et al.). The authors found that excitatory stimulation of the RpSMA and inhibitory stimulation of the MCV6 enhanced reaction speed in simple tasks but did not significantly impact more complex cognitive tasks. Furthermore, a systematic review by Wu et al. examined the effects of tACS on working memory, learning ability, and decision-making. The findings suggested that tACS enhances cognitive performance in athletes and healthy individuals, with effectiveness dependent on stimulation frequency, phase, area, and dose, highlighting the need for further research into individual differences in neurostimulation efficacy.

Semantic cognition, or the ability to process and retrieve meaningful information, has also been explored in neurostimulation research. A meta-analysis investigating whether TMS could simulate deficits in semantic control by targeting key brain regions involved in semantic retrieval found no significant effects of TMS after correcting for publication bias via a suite of methods (Funnel plots, Trim and Fill, Eggers Regression and Rank Correlation test, Selection Models, and Z curve analysis), suggesting that TMS may not be as effective for disrupting semantic processing as previously assumed (Ambrosini et al.). This calls for methodological improvements in future studies, including consideration of stimulation intensity, waveform and entrainment to underlying neural activity to enhance the reliability of findings in this area.

Psychological effects of neurostimulation

Researchers have also explored whether neurostimulation can modulate cognitive dissonance, the well-documented psychological discomfort experienced when making difficult choices. A study using tDCS to inhibit the posterior medial frontal cortex (pMFC) found reduced preference changes in rejected options, while excitatory anodal stimulation showed no significant effect (Rybina et al.). These results highlight the potential of neurostimulation to influence decision-making processes, although the exact mechanisms require further investigation.

Finally, neurostimulation has also been explored in addressing attention deficits, particularly in individuals with conditions like attention-deficit/hyperactivity disorder (ADHD). A randomized controlled trial by Cheung et al. investigated the efficacy of transcranial pulse stimulation (TPS) for treating ADHD in young adolescents. The study demonstrated that TPS led to a 30% reduction in ADHD symptoms, with sustained benefits up to 3 months post-intervention. Despite not reporting standardized effect sizes which would greatly assist in the methodological and statistical reporting clarity the work highlights the utility of various forms of neurostimulation for not only cognitive enhancement, but as pharmacological interventions as well. Future work should examine the longer term benefits (e.g., 6–12 months) and or the requirement for maintenance neurostimulation sessions.

Future applications for neurostimulation

Beyond traditional cognitive tasks, neurostimulation is being applied in realistic virtual environments to study its effects on human behavior. A review on tDCS in driving and flight simulators found that stimulation could enhance performance in specific tasks, such as maintaining safe driving distances or executing precise landings (Sansevere and Ward). However, the effects were highly context-dependent, influenced by factors such as participant

expertise, task complexity, and the targeted brain region, again highlighting the need for further research to generalize findings across a broader range of real-world applications.

Conclusion

Neurostimulation is a rapidly evolving field with significant implications for cognitive and perceptual enhancement. While studies have demonstrated its potential in improving attention, memory, decision-making, and learning, several factors—such as individual differences, task complexity, and ethical considerations—need to be addressed. Personalized neurostimulation protocols, methodological refinements, and regulatory frameworks will be crucial in ensuring the effective and responsible application of these technologies. As research advances, neurostimulation may become an integral tool for cognitive enhancement in both clinical and everyday settings, bridging the gap between neuroscience and real-world applications.

Author contributions

AT: Conceptualization, Funding acquisition, Investigation, Project administration, Writing – original draft, Writing – review & editing. AB: Writing – review & editing. MC: Investigation, Resources, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The moderating effects of sex, age, and education on the outcome of combined cognitive training and transcranial electrical stimulation in older adults

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Computerized cognitive training (CCT) has been shown to improve cognition in older adults via targeted exercises for single or multiple cognitive domains. Combining CCT with non-invasive brain stimulation is thought to be even more effective due to synergistic effects in the targeted brain areas and networks. However, little is known about the moderating effects of sex, age, and education on cognitive outcomes. Here, we investigated these factors in a randomized, double-blind study in which we administered CCT either combined with transcranial direct (tDCS), alternating (tACS) current stimulation or sham stimulation. 59 healthy older participants (mean age 71.7±6.1) received either tDCS (2mA), tACS (5Hz), or sham stimulation over the left dorsolateral prefrontal cortex during the first 20min of a CCT (10 sessions, 50min, twice weekly). Before and after the complete cognitive intervention, a neuropsychological assessment was performed, and the test scores were summarized in a composite score. Our results showed a significant three-way interaction between age, years of education, and stimulation technique ($F_{(6,52)}$=5.53, p=0.007), indicating that the oldest participants with more years of education particularly benefitted from tDCS compared to the sham group, while in the tACS group the youngest participants with less years of education benefit more from the stimulation. These results emphasize the importance of further investigating and taking into account sex, age, and education as moderating factors in the development of individualized stimulation protocols.

Clinical Trial Registration: ClinicalTrials.gov, identifier NCT03475446.

KEYWORDS

older adults, tDCS, tACS, cognitive training, education, age, sex

1. Introduction

Transcranial electrical stimulation (tES) has been used in various studies to improve cognitive performance in healthy participants and diverse patient populations (Yavari et al., 2018).

Transcranial direct current stimulation (tDCS) is one type of tES which has been frequently used in single sessions or repeatedly with and without concurrent tasks. Today, tDCS is mostly

combined with a concurrent task to benefit from synergistic effects of stimulation and intrinsic brain activity (Indahlastari et al., 2021). When tDCS is applied repeatedly with cognitive stimulation in the course of a cognitive intervention the outcomes were promising in cognitive domains like working memory and cognitive control (Elmasry et al., 2015). A recent study reported contrary effects of anodal tDCS in middle aged (50–64 years) and older (65–81 years) adults. While older adults showed better recognition performance after stimulation over the left dorsolateral prefrontal cortex (DLPFC) during encoding, middle aged adults performed worse (Bagattini et al., 2023). Computerized cognitive training (CCT) of working memory and concurrent stimulation moreover benefitted older adults more than young adults (Pergher et al., 2022). Similarly, when comparing younger-old and older-old participants in a combined working memory training and tDCS study, Assecondi et al. (2022) found that older-old with lower working memory capacity profited more from tDCS during working memory training, whereas younger-old with high working memory scores performed significantly better without concurrent tDCS. Age-related brain changes, namely atrophy, lead to an increase in cerebrospinal fluid volume, which in turn affects the direction and the strength of the electrical field reaching the targeted region of interest (Bhattacharjee et al., 2022). For tDCS, this might indicate that stronger currents have to be applied to achieve stimulation effects in older adults. On the other hand, changes in the neurotransmitter system in older adults might increase the efficacy of tDCS even when neuroplasticity decreases over the lifespan (Habich et al., 2020). Despite general age-related brain changes there exist large differences on the individual level caused by environmental and genetic factors (Franke and Gaser, 2019). While this variability supports the inclusion of age as moderating factor in the analysis of tES effects, we were not able to identify such effects in our study combining different tES protocols and CCT (Krebs et al., 2021). Notably, age-related brain changes differ between females and males, pointing out sex as another factor moderating brain stimulation outcomes (Bhattacharjee et al., 2022). However, there are tDCS studies not reporting any sex differences in older adults, see Hayek et al. (2021) for example. Finally, years of education might be another moderating factor for stimulation outcomes. For example, Berryhill and Jones (2012) found that only healthy older adults with more years of education benefitted from stimulation during a working memory task. Years of education are a common proxy of cognitive reserve, which can also be estimated by questionnaires like the cognitive reserve index questionnaire (Nucci et al., 2012). In mild cognitive impairment, we found in a previous study that higher cognitive reserve was associated with stronger tDCS effects, similar as has been reported in the study by Berryhill and Jones (2012), while in Alzheimer's dementia reverse findings were reported in an episodic memory task (i.e., stronger tDCS effects in individuals with low cognitive reserve) (Krebs et al., 2020). Different approaches, i.e., investigating both education as well as cognitive reserve, might help to elucidate moderating effects differently in various populations. Overall, the results across studies show a large heterogeneity. Apart from differences in study design it seems that also inter-individual differences moderate the efficacy of tDCS, for example age, baseline cognition, years of education, and sex (Koo et al., 2023).

Another tES technique is transcranial alternating current (tACS) stimulation, which involves applying alternating electrical currents in sinusoidal waves at certain frequencies. By targeting specific frequencies, tACS aims to adapt intrinsic brain oscillations and hereby influence cognitive and behavioral functions (Antal and Herrmann, 2016). Stimulation at theta frequency (4–8 Hz) appears to be beneficial for several cognitive processes (Antal and Herrmann, 2016; Antonenko et al., 2016) and gamma tACS (*ca.* 40 Hz) seems to play a crucial role in memory processes and appears to be a promising avenue to alleviate memory impairments in dementia (Manippa et al., 2023). To date, tACS has only rarely been used in combination with CCT. In healthy older adults CCT combined with theta tACS did not result in improvements in multitasking performance on the group level. However, there was a high inter-individual variability indicating that there are likely additional factors at play such as baseline peak theta frequency (Zanto et al., 2021). Another study found that higher age was beneficial when theta tACS was applied during an associative memory task compared to a single session of sham stimulation (Klink et al., 2020). In older adults with mild cognitive impairment a single session of gamma tACS (40 Hz) was more beneficial for executive functions (as assessed with the Stroop task and the Trail-Making-Test) than tDCS (Kim et al., 2021). Grover et al. (2022) found improvements in working memory, after stimulating the prefrontal (gamma tACS) versus the parietal cortex (theta tACS) for 4 days in older healthy adults with effects lasting for 1 month. Notably, participants with lower baseline cognitive functions improved more. Exploratory analysis furthermore revealed stronger effects in males than females, but after correcting for multiple comparisons this finding did not hold. Another study reported a beneficial effect of gamma tACS on episodic memory in subjects with Alzheimer's disease, but no effect of cognitive reserve as measured with the cognitive reserve index questionnaire (Benussi et al., 2022). Finally, a recent meta-analysis supports positive findings for several cognitive functions and emphasizes stronger effects after offline compared to online tACS (Grover et al., 2023). In young adults, CCT of executive functions (working memory, inhibitory control, cognitive flexibility) in combination with multifocal gamma tACS (40 Hz) did not show an improvement in fluid intelligence (Brem et al., 2018). Another study in young adults showed no sex differences when alpha tACS was applied at the individual alpha frequency on the performance in a mental rotation task, while a significant interaction between stimulation group and sex was found for fluid intelligence (Kasten and Herrmann, 2017). Further analysis showed a trend ($p < 0.09$) for a negative effect of tACS in the individual alpha frequency on fluid intelligence in males (Pahor and Jaušovec, 2016).

Our aim was to investigate the moderating effects of age, years of education, and sex alone as well as their interactions in a cognitive intervention combining CCT with tDCS, tACS, or sham stimulation. Based on previous studies, we hypothesised that stimulation effects would be stronger in individuals with more years of education. We moreover investigated possible moderating effects of cognitive reserve on stimulation outcomes to investigate if potential moderating effects of education on stimulation can be confirmed with this measure. For sex, the limited amount of data, which was moreover mostly collected in young adults, prevented the formulation of a directed hypothesis. Despite our previous nil-findings regarding an effect of age on stimulation outcomes (Krebs et al., 2021), we hypothesised significant effects when considering more complex relationships (i.e., between age and sex or age and education).

2. Methods

2.1. Study design and participants

The present study was part of a larger study investigating the effect of CCT combined with transcranial electrical stimulation in a double-blind, sham-controlled, and parallel group design (Krebs et al., 2021). Participants were randomly assigned to one of the three stimulation conditions (tDCS, tACS, or sham) prior to their first on-site visit. The final sample contained 59 healthy older participants (mean age 71.7 ± 6.1, range: 61–85; 31 male; years of education median: 14, range: 9–25; see Figure 1 for a flow diagram of participants).

The eligibility criteria were the following: healthy participants (based on self-reports aged between 60 and 85 years, native or fluent German speaker, normal or corrected to normal vision and hearing, and written informed consent). The exclusion criteria were: any history of seizure or stroke, traumatic brain injury, current psychiatric or neurological disorders, substance abuse, metal implants in the head, pacemaker, smoking, psychotropic medication, severe tinnitus and self-reported left-handedness. The study was approved by the local ethics committee (Nr. 2017-02056) and performed in accordance with the Declaration of Helsinki and registered on ClinicalTrials.gov (NCT03475446). Participants gave their written informed consent before study onset.

2.2. Cognitive assessments and questionnaires

The cognitive assessment was performed at baseline (i.e., within 6 weeks before intervention onset) and repeated within 2 weeks after the cognitive intervention (except for three participants for whom the delay between the last training and the post-assessment was more than 30 days due to vacations or illness). We used the computerized Vienna Test System (Schuhfried GmbH, Mödling, Austria) to assess verbal and non-verbal memory functions (auditory word list learning: learning sum, delayed recall, d prime (Pallier, 2002), word recognition; continuous figural recognition: d prime), attention functions (divided and selective attention: d prime), and executive functions (inhibition: d prime Go/NoGo; semantic/lexical fluency: total number of words; working memory: block span backwards). Baseline motivation was assessed with the objective achievement motivation test (Brandstätter, 2005). Further executive and attention functions were assessed with paper-pencil tests [5-point test: number of unique designs (Regard et al., 1982); number connection test: average time (Oswald and Roth, 1987)]. Parallel test versions were used whenever available (i.e., MoCA, auditory wordlist learning, fluency, and number connection tests). The primary cognitive outcome was a cognitive composite score that was based on principal component analysis on test scores from the pre-assessment. All scores except the inhibition test scores were included in this cognitive composite score [see Krebs et al. (2021) for single test scores]. To build the composite score, individual raw test

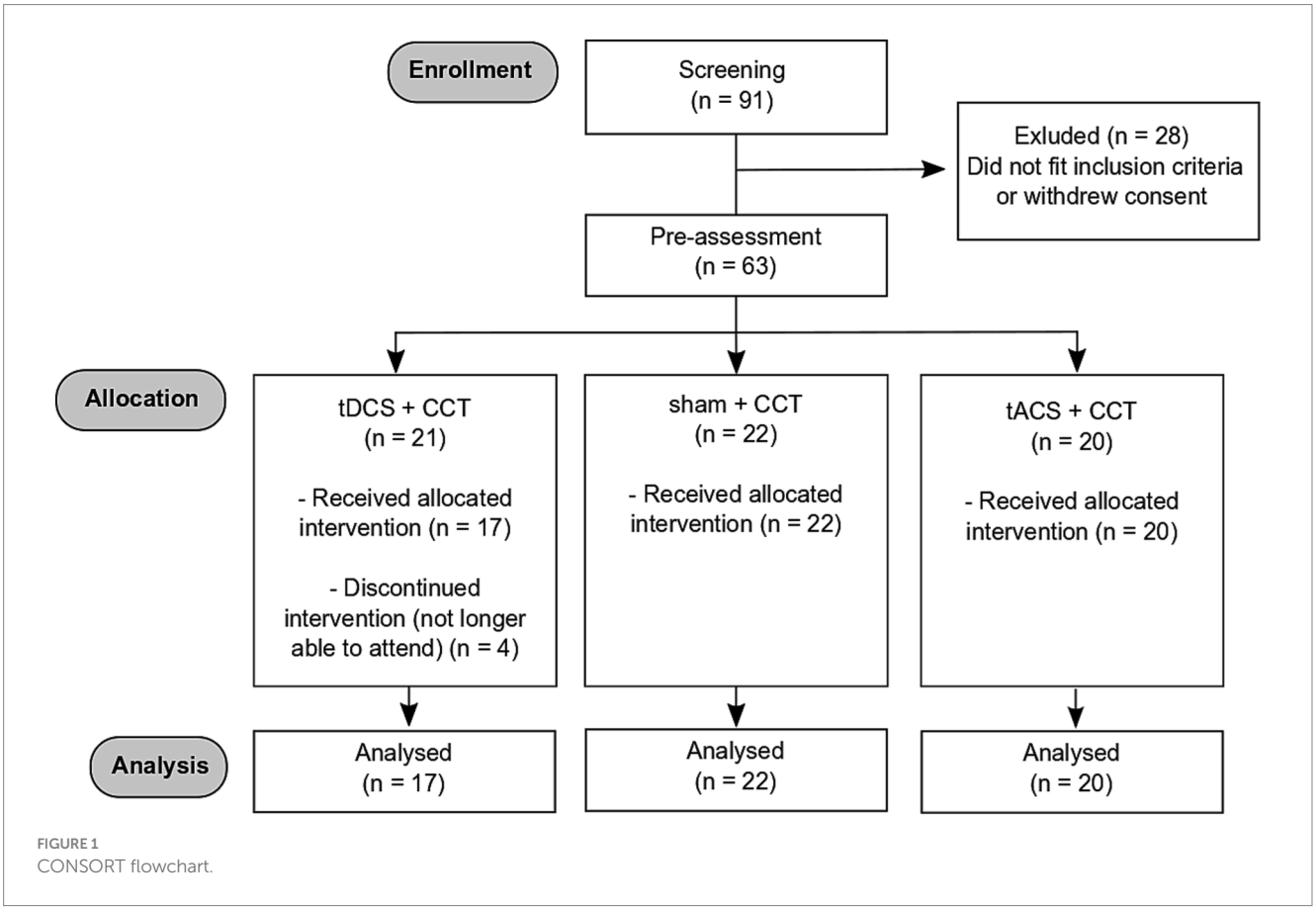

FIGURE 1
CONSORT flowchart.

scores were scaled to the respective test score from the baseline assessment and then the mean across tests from one time point (i.e., test scores from pre and post assessment) was calculated to calculate the final composite score. Furthermore, participants completed the cognitive reserve index questionnaire (CRIq) (Nucci et al., 2012) and the MoCA.

2.3. Intervention: computerized cognitive training combined with non-invasive brain stimulation

The intervention consisted of CCT (10 sessions, 50 min, twice weekly at least 2 days apart) combined with either tDCS (2 mA), theta tACS (1 mA, 5 Hz, 0° initial phase shift), or sham stimulation during the first 20 min of each CCT session (DC-Stimulator PLUS, NeuroConn GmbH, Ilmenau, Germany). We hereby kept to previously used stimulation durations (i.e., 20 min) to ensure maximal effects and hypothesised that prolonged stimulation effects would also support the training outcomes of tasks accomplished immediately after the end of the stimulation (Nitsche and Paulus, 2000; Elyamany et al., 2021). We therefore combined online and offline training within one session to also ensure a sufficient length of cognitive training. Sessions twice weekly over a period of 5 weeks were chosen as this corresponds to a typical clinical pattern for the administration of long-term interventions. Twice weekly sessions could be easily implemented in a routine setting and would be more feasible for participants than for example daily sessions. The sessions were performed in groups of three to six participants. The anode was placed over the left dorsolateral prefrontal cortex [5×7 cm, F3 according to the 10–20 EEG system (Klem et al., 1999)], the cathode (10×10 cm) was placed over the right supraorbital area (orientation as indicated in Figure 2). The ramping up/down time was 15 s in all stimulation groups and the stimulation setup allowed double blinding.

During the CCT participants trained processing speed, selective and divided attention, and executive functions (spatial working memory, inhibitory control) with the "CogniPlus" software (Schuhfried GmbH, Mödling, Austria). The tasks were displayed on 22-Inch desktop screens and the answers logged via simplified keyboards provided by the software company. During the stimulation participants trained either selective or divided attention. After the attention task, the stimulation electrodes were removed during a short break of approximately 10 min. In the second part of the session the participants performed two out of three tasks to train either spatial working memory, executive functions (inhibitory control) or speed of processing for 15 min each.

The study design is shown in Figure 2.

2.4. Statistical analyses

In the original study (Krebs et al., 2021) we found beneficial effects of tDCS in participants with low MoCA scores and no interaction between age and stimulation (Krebs et al., 2021) using linear mixed models. In the present study, we adopted a different analysis method, following recommendations from a study investigating which dependent and independent variables in a linear regression are best suited to predict the success of a CCT (Mattes and Roheger, 2020). According to Mattes and Roheger (2020) the best model includes baseline performance as one predictor, in combination with an interaction term between treatment outcome and predictor of interest (e.g., age). As outcome, the absolute change score is a valid choice (Mattes and Roheger, 2020). In the present study, we included the composite score at baseline in all models to address potential pre-existing differences in cognition. Values for age and years of education were mean centered and standardized. To further investigate significant interaction effects, we addressed different scores in age and years of education in further regression models (mean age ± 1 SD for younger and older age; mean years of education ±1 SD for few and many years of education). These further analyses allowed us to investigate interaction terms with a specific focus on certain factor levels. For descriptive statistics, we separated the sample according to age tertiles (youngest-old, middle-old, oldest-old) and performed Kruskal-Wallis tests for investigating differences between all tertiles or *t*-tests when comparing only lowest and highest tertiles. To explore potential associations between age, sex, and years of education we performed correlation analyses before the linear regression models. Treatment outcome in the linear regression models was the composite score difference, i.e., post-intervention composite score – pre-intervention composite score. To confirm the previously reported non-significant interaction between stimulation technique and cognitive improvement through the CCT (Krebs et al., 2021), we repeated this previous analysis using the method described above. Additionally, we repeated the models including years of education with the total score of the cognitive reserve questionnaire. Using the novel analysis approach, we confirmed the non-significant results including education as moderating factor (Supplementary material). To explore the interaction between years of education, sex or age and stimulation in the present study, we first performed regression models investigating two-way interactions. Given that there might exist interactions in between moderating factors, we also analysed three-way interactions (i.e., two moderating factors plus stimulation) in a next step. Interaction terms which showed a tendency towards significance (i.e., *p*-values between 0.05 and 0.10) were further analysed with additional regression models corresponding to those for significant interactions. As our analyses were explorative, we did not correct *p*-values for the number of performed regression models.

3. Results

First, we investigated differences between age groups. The age groups did not differ in years of education or sex, however, they differed significantly in baseline composite score and composite difference scores (Table 1). The overall mean score from the Montreal Cognitive Assessment was 26.31 (SD ± 2.62, min = 21, max = 30), which is above the cut-off score of 22 for cognitive disorders (Freitas et al., 2012). There were no correlations between age and years of education ($r = -0.07$, $p = 0.58$) or age and sex ($r = 12$, $p = 0.36$). On average, males had more years of education (mean: 16 years) than females (13.57 years) ($t = 2.85$, $p = 0.006$).

Overall, a paired *t*-test showed that the cognitive intervention was successful in improving the composite score regardless of the stimulation group ($t = -6.18$, $p < 0.001$). However, the linear regression model did not show any significant effect of stimulation group on

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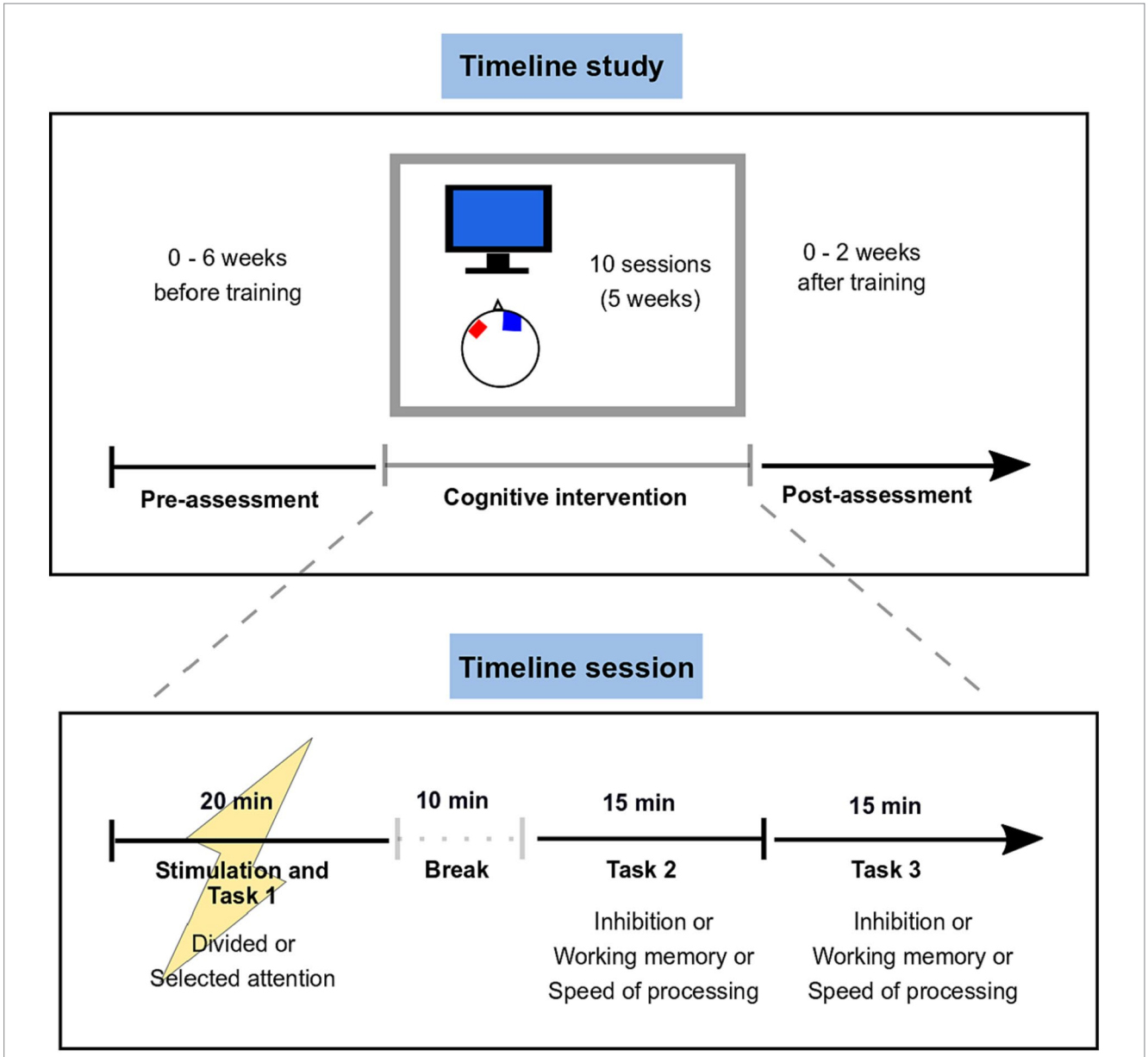

FIGURE 2
Study design. Participants underwent the pre-assessment (neuropsychological test battery and questionnaires) within 6 weeks before the intervention and completed the post-assessment within 2 weeks after the end of the intervention. During each of the 10 sessions, the CCT was combined with either tDCS, tACS, or sham stimulation during the first 20 min of the trainings. After a 10 min break and removal of the stimulation electrodes, they continued the cognitive training with two further tasks targeting one of three cognitive domains (inhibition, spatial working memory, processing speed).

TABLE 1 **Descriptive statistics of different age groups.**

	Youngest – Old (n = 20)	Middle – Old (n = 20)	Oldest – Old (n = 19)	p-value
Age (years)	65.15 (± 2.37)	71.65 (± 1.35)	78.74 (± 3.30)	**<0.001**[a]
Years of education	14.60 (± 3.76)	15.50 (± 3.40)	14.42 (± 3.37)	0.47[a]
Sex	10 males	12 males	9 males	0.71[a]
Baseline composite score	0.20 (± 0.54)	0.15 (± 0.57)	−0.38 (± 0.57)	**<0.001**[a]
Difference score	0.23 (± 0.20)	0.11 (± 0.25)	0.33 (± 0.33)	**0.03**[a]
MoCA score	27.2 (2.26)	26.3 (2.64)	25.4 (2.75)	0.09[a]

Mean values and standard deviations are reported. sham, sham stimulation; tDCS, transcranial direct current stimulation; tACS, transcranial alternating current stimulation; MoCA, Montreal cognitive assessment; n, number of participants; [a]Kruskal-Wallis test, significant values (p<.05) are bold.

composite score difference ($F_{(55,2)} = 6.04$, $p = 0.15$) confirming the previously reported results.

Regardless of the respective stimulation group, participants with fewer years of education (lowest tertile) improved more in the cognitive composite score than participants with more years of education (highest tertile) ($t_{(30.68)} = 2.57$, $p = 0.02$). There was no similar effect when comparing the lowest and highest tertiles in age ($t_{(30.68)} = -1.13$, $p = 0.27$) or when comparing females and males in the complete sample ($t_{(56.02)} = -0.98$, $p = 0.33$).

The regression model investigating the association between age and stimulation did not show a significant interaction ($F_{(6,52)} = 2.38$, $p = 0.10$). Further regression analysis showed a significant tDCS effect in oldest participants compared to sham stimulation ($t = 2.79$, $p < 0.001$). The other models did not show an interaction between sex and stimulation ($F_{(6,52)} = 1.87$, $p = 0.16$) or years of education and stimulation.

The regression model including the three-way-interaction between years of education*age*stimulation showed a significant interaction ($F_{(12,46)} = 5.53$, $p = 0.007$). Compared to sham, tDCS was most beneficial in the oldest and highest educated participants ($\beta = 68$, $t = 4.01$, $p < 0.001$) while in the youngest individuals with fewest years of education tACS showed a tendency for beneficial effects ($\beta = 25$, $t = 1.95$, $p = 0.058$) (Figure 3A). The model including the three-way-interaction between years of education*sex*stimulation did not show a significant interaction ($F_{(12,46)} = 2.12$, $p = 0.13$), while the model including age*sex*stimulation showed a trend towards significance ($F_{(12,46)} = 2.56$, $p = 0.09$). When data was separated by sex and the regression models were repeated, younger and average aged females showed a significant tACS effect (younger females: $\beta = 0.36$, $t = 3.10$, $p < 0.05$; average aged females: $\beta = 0.17$, $t = 2.11$, $p < 0.05$) and a tDCS effect was present in older and average aged males (average aged males: $\beta = 0.32$, $t = 2.65$, $p = 0.01$; older males: $\beta = 0.67$, $t = 4.08$, $p < 0.001$) compared to sham stimulation (Figure 3B).

There was no difference in side effects between stimulation groups and blinding was successful [see Krebs et al. (2021) for details].

4. Discussion

The aim of our analyses was to investigate the moderating effects of age, years of education, and sex on a cognitive intervention combining CCT with different tES protocols (tDCS, tACS, and sham). While there were no interactions between each of the single factors and the stimulation group in two-way interactions, we found a significant three-way interaction between years of education, age and stimulation. Furthermore, there was a tendency towards significance in the interaction between sex, age, and stimulation.

Our examinations of the three-way interaction (years of education, age and stimulation) showed, that especially older participants with more years of education benefitted from tDCS, while in young adults with fewer years of education tACS seemed more promising to augment the effect of a CCT. Regarding tACS, beneficial effects on long term memory were observed after high-definition stimulation over the left DLPFC with gamma tACS up to 1 month. Theta tACS over the left inferior parietal lobe showed beneficial effects in a working memory task in older adults in the same study. Interestingly, this tACS effect was strongest in participants with low cognitive performance, as assessed with the MoCA (Grover et al., 2022). The design of the present study and those of Grover et al. (2022) are different in many ways (e.g., stimulation site, electrode type, stimulation schedule), which might account for the differing findings. Our finding of a tendency towards significance in younger participants with fewer years of education should be confirmed in further studies. Regarding the efficacy of tDCS, we suggested in previous research that tDCS is likely not beneficial when brain functions are optimal but rather becomes effective when a crucial level of cognitive decline is reached (Krebs et al., 2020, 2021). In the oldest adults in the sham group the improvement in the composite score difference became smaller or even negative with more years of education while the opposite pattern was visible in the tDCS group. It is possible, that in oldest participants more years of education led to optimized cognitive processes or implicit strategies to solve cognitive tasks which cannot be further improved through CCT itself. However, it is possible that the synergistic effects of CCT and brain stimulation allow a further increase in performance through more efficient cognitive processes. During anodal tDCS a certain brain region is targeted which is expected to become more active through the stimulation (Polanía et al., 2018). In the present study we targeted the left DLPFC, which is thought to be a hub for executive control processes and a brain area that is widely connected to various other brain regions such as the parietal lobe or the hippocampus (Hertrich et al., 2021; Smucny et al., 2022). Especially the left DLPFC has been stimulated successfully to increase performance in previous studies targeting different cognitive domains (Mancuso et al., 2016; de Lara et al., 2017). Regarding our findings, it is possible that tDCS increased cognitive control processes. Those improved control processes could positively affect brain networks or task solving strategies, which are predominantly used by individuals with more years of education and lead to larger training benefits. The positive effect of tDCS over the DLFPC in older adults with more years of education was also reported in another study using a working memory paradigm. The authors assumed that this result is caused by different strategies in higher educated participants resulting in a better recruitment of the prefrontal cortex (Berryhill and Jones, 2012). One study (Assecondi et al., 2022) even reported that younger-old with higher baseline working memory capacity performed significantly better during working memory training without concurrent tDCS. Although our results numerically pointed towards the same direction for the youngest-old with high education, we could not confirm this previous finding statistically.

Interestingly, when scores from the cognitive reserve questionnaire were used in the linear regression model instead of years of education, there was no significant interaction. Both measures correlate significantly in our data ($r = 0.50$, $p < 0.001$) and years of education can be seen as a proxy of cognitive reserve (Mungas et al., 2018). One difference between both measures is, that the total score of the cognitive reserve questionnaire also includes subscales which address leisure time activities as well as working activity. Additionally, the scores calculated for the respective subscales are based on a formula and do not correspond to the sum of years. It is possible, that for identifying the moderating factors of non-invasive brain stimulation in healthy older adults an unprocessed proxy like number of years better represents the neural substrate of cognitive reserve than a more complex measure like questionnaire scores.

Because the three-way interaction including stimulation, sex, and age showed a trend towards significance, we performed further

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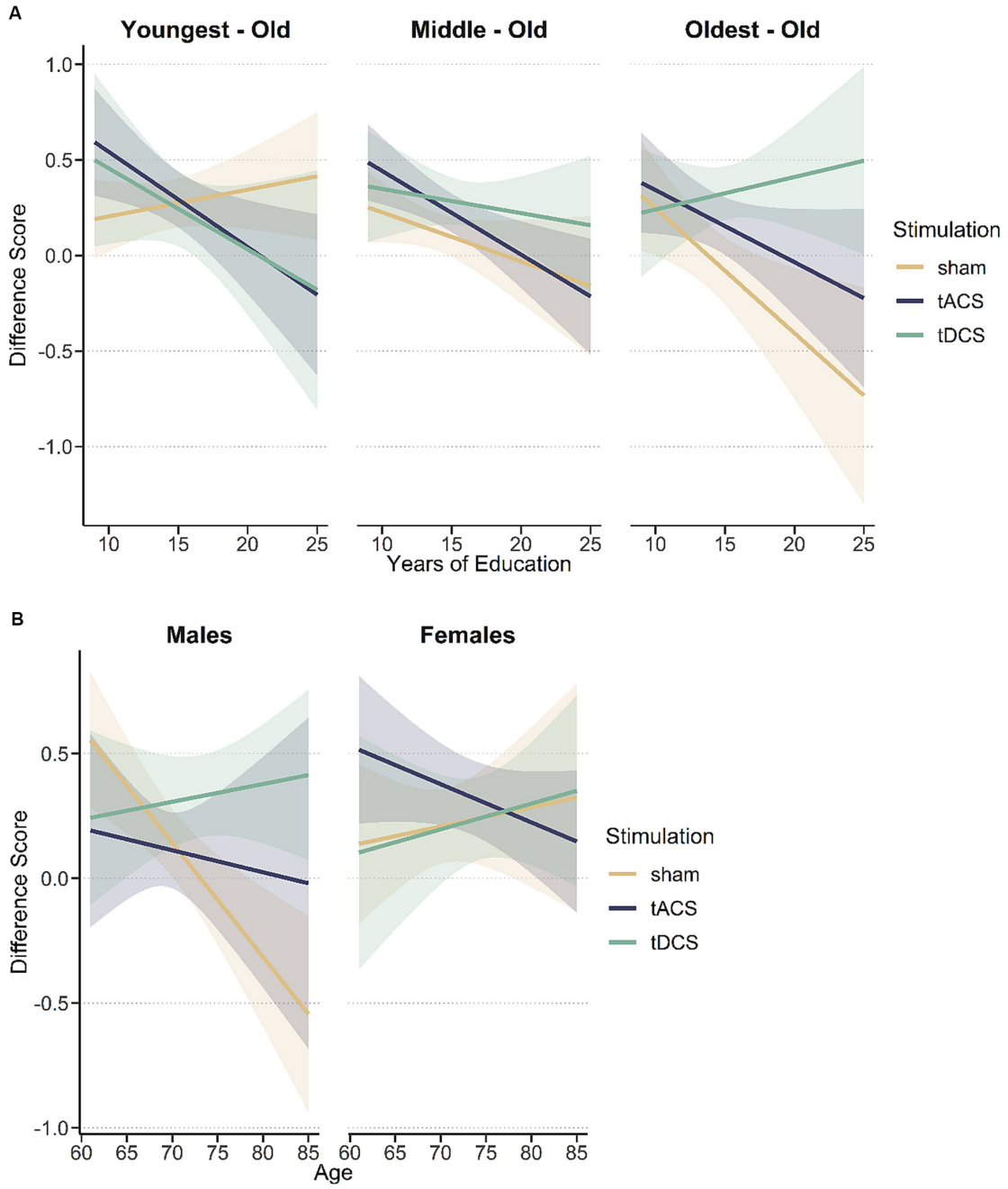

FIGURE 3
(A) Significant three-way interaction between age, years of education, and stimulation on composite score differences. There is a positive tDCS effect in oldest adults while in youngest adults tACS might have some beneficial effects. **(B)** There was a trend ($p = 0.9$) for a significant interaction between sex, age and stimulation on composite score differences. TDCS might be beneficial in oldest males, while tACS seems to support the efficacy of the cognitive training in youngest females.

analyses which showed that males benefit more from tDCS if they are older. Therefore, it is possible that also the beneficial effect of tDCS in the previously reported interaction (stimulation, years of education, and age) was mainly driven by oldest males with many years of education. As there was not enough data to perform additional statistical analyses when the sample was split according to age tertiles, we inspected descriptive statistics to estimate if this assumption might be true. Actually, in the oldest-old tDCS group males improved more but had fewer years of education (composite score difference: 0.51, years of education: 15.3 years) than in the sham group (composite score difference: −0.13, years of education: 18 years). Therefore, we assume that more years of education support tDCS effects regardless of sex. For youngest females in our sample, it seems that tACS led to more benefits of the CCT. This is in line with previous research which found a positive effect of tACS in young adult females (Pahor and Jaušovec, 2016).

While the sample size of 59 participants seems appropriate, it provides only limited data for subgroups, especially if multiple

attributes are combined. Additionally, the trend for positive tACS effects in youngest adults with low education should be further investigated in young samples in a cognitive intervention. Given the explorative purpose of our analyses, we did not correct *p*-values for the number of performed regression models, which might lead to an overestimation of our results. As we aimed to include also participants with few years of education and across a considerably broad age range of 25 years, we did not define MoCA scores below a certain cut-off score as exclusion criteria. Therefore, we included three participant which are healthy based on self-reports, but the MoCA indicates that some cognitive impairment might be present.

In conclusion, there exist complex interactions between individual characteristics affecting the outcome of CCT combined with tES. Our findings indicate that tDCS might be most beneficial in oldest and highest educated individuals or males regardless of years of education. In youngest females in our sample, it seems that the combination of a CCT and tACS might lead to improvements in cognitive outcomes. These results emphasize the importance of further investigating and considering sex, age, and education as moderating factors in the development of individualized stimulation protocols.

Data availability statement

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

Ethics statement

The study was approved by the Kantonale Ethikkommission Bern, Switzerland (Nr. 2017-02056) and was conducted in accordance with the local legislation and institutional requirements. Participants gave their written informed consent before study onset.

Author contributions

SK, CK, JP, and A-KB designed the research project. CK was responsible for data collection with support from EB. CK performed the data analysis. CK and A-KB drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2023.1243099/full#supplementary-material

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Effects of repetitive transcranial magnetic stimulation on episodic memory in patients with subjective cognitive decline: study protocol for a randomized clinical trial

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Introduction: Early decline of episodic memory is detectable in subjective cognitive decline (SCD). The left dorsolateral prefrontal cortex (DLPFC) is associated with encoding episodic memories. Repetitive transcranial magnetic stimulation (rTMS) is a novel and viable tool to improve cognitive function in Alzheimer's disease (AD) and mild cognitive impairment, but the treatment effect in SCD has not been studied. We aim to investigate the efficacy of rTMS on episodic memory in individuals with SCD, and to explore the potential mechanisms of neural plasticity.

Methods: In our randomized, sham-controlled trial, patients (n = 60) with SCD will receive 20 sessions (5 consecutive days per week for 4 weeks) of real rTMS (n = 30) or sham rTMS (n = 30) over the left DLPFC. The primary outcome is the Auditory Verbal Learning Test-Huashan version (AVLT-H). Other neuropsychological examinations and the long-term potentiation (LTP)-like cortical plasticity evaluation serve as the secondary outcomes. These outcomes will be assessed before and at the end of the intervention.

Discussion: If the episodic memory of SCD improve after the intervention, the study will confirm that rTMS is a promising intervention for cognitive function improvement on the early stage of dementia. This study will also provide important clinical evidence for early intervention in AD and emphasizes the significance that impaired LTP-like cortical plasticity may be a potential biomarker of AD prognosis by demonstrating the predictive role of LTP on cognitive improvement in SCD.

Ethics and dissemination: The study was approved by the Human Research Ethics Committee of the hospital (No. 2023-002-01). The results will be published in peer-review publications.

Clinical trial registration: https://www.chictr.org.cn/, identifier ChiCTR2300075517.

KEYWORDS

episodic memory, subjective cognitive decline, dorsolateral prefrontal cortex, repetitive transcranial magnetic stimulation, trial protocol

1. Introduction

Alzheimer's disease (AD), a neurodegenerative disorder of great concern in the context of the aging population, has come to be viewed not only as an isolated clinical diagnosis but as a multilevel process that changes along a sequential spectrum (Aisen et al., 2017). The earliest clinical manifestation in the spectrum of AD is subjective cognitive decline (SCD), also known as self-experienced memory disturbance without objective cognitive impairment (Wang et al., 2020). SCD is of great value when considered as an elevated risk factor for the development of AD dementia (Wolfsgruber et al., 2017; Wang et al., 2020), given that approximately 14.1% of individuals with SCD develop dementia in 4-year follow-up studies (Mitchell et al., 2014). These pathophysiologic changes occur many years before clinical signs of AD and it is likely that effective therapies at the stage of SCD will have the potential to slow or even halt the progression to AD (Si et al., 2020; Wang et al., 2020). Thus, SCD may be of utmost importance as a time node for early interventions in AD [6]. Based on the accumulating evidence from previous meta-analysis findings, non-pharmacological interventions have been widely used in individuals with SCD (Sheng et al., 2020).

Repetitive transcranial magnetic stimulation (rTMS), as a safe and reliable non-pharmacological intervention, has been shown to result in significant cognitive improvement in AD and mild cognitive impairment (MCI) in many research studies (Lin et al., 2019; Chou et al., 2020; Jiang et al., 2020). To date, rTMS over the left dorsolateral prefrontal cortex (l-DLPFC) has been shown to be an effective method of treatment in AD (Level C of evidence) (Di Lazzaro et al., 2021). The l-DLPFC is the most common choices for single site rTMS stimulation. A number of studies which targeted the l-DLPFC have shown significant improvements in cognitive function scores (Hauer et al., 2019; Lin et al., 2019; Zhang et al., 2022).

Episodic memory (EM) represents the ability to recall and recognize previously encountered objects, people, and events, and serves as a process that is critical for advanced cognitive functions such as judgment and decision-making (Wang, 2021; Lalla et al., 2022). In some studies, EM has been found to be a potentially sensitive indicator for pathological conditions such as AD (Tromp et al., 2015; Xue, 2018; Yu et al., 2021). It is also possible that EM may already be impaired relative to healthy controls (HC) in the SCD stage using the Auditory Verbal Learning Test-delayed recall (AVLT-DR), even when standardized memory tests show no decline (Zhu et al., 2021). Transcranial direct current stimulation (tDCS) and rTMS studies have shown that the dorsolateral prefrontal cortex (DLPFC) region plays an important role in strengthening EM associative memory and recall via reconsolidation in patients with dementia (Solé-Padullés et al., 2006; Vaqué-Alcázar et al., 2021). One previous research has demonstrated that the application of anodal tDCS on the left lateral prefrontal cortex (PFC) enhances pre-existing episode memories, with the effect persisting for a period of 30 days in elderly individuals with SCD (Manenti et al., 2017). Nonetheless, these results demonstrate the ability of the interventions to transiently influence brain function and did not identify them as therapeutic tools for individuals with memory impairment who performed poorly on neuropsychological tests (Solé-Padullés et al., 2006; Vaqué-Alcázar et al., 2021; Cotelli et al., 2022). Thus, to date, the efficacy of rTMS as a therapeutic tool for patients with SCD requires further investigation.

Previous studies have reported the varied neural mechanisms of rTMS for ameliorating cognitive impairment. rTMS may not only regulate the regulation of cortical excitability but may also lead to changes in cerebral blood flow, and neurotransmitters as well as the level of brain derived neurotrophic factor. Most importantly, rTMS may also alter synaptic plasticity and brain networks (Griskova et al., 2006). A Long-term potentiation (LTP) is one of the most extensively studied forms of synaptic plasticity (Wichmann and Kuner, 2022), and is the key cellular basis of the learning and memory process, which can be induced and evaluated simply by transcranial magnetic stimulation (TMS) protocols (Di Lorenzo et al., 2020b; Di Lazzaro et al., 2021). Large studies of patients with AD have demonstrated that changes in the LTP mechanism are linked to memory loss and increased levels of CSF tau. This association is particularly strong when coupled with the apolipoprotein E gene (APOE) ε4 polymorphism and progression of the disease (Francesco and Koch, 2021). Therefore, considering its potential as a biomarker for assessing synaptic impairment, TMS-assessed LTP may provide reliable information about related physio-pathological events in AD. Higher levels of CSF t-Tau of individuals with AD are linked with more powerful inhibition of motor evoked potentials, as induced by the 1 Hz TMS protocol (Koch et al., 2011). Moreover, LTP may be a as a predictive tool for revealing the progression of cognitive decline across the spectrum of AD (Motta et al., 2018). Previous studies have found that participants with MCI and amyloid positivity showed abnormal LTP-like plasticity with poorer memory function (Buss et al., 2020). These findings indicate the potential for utilizing LTP as a prognostic indicator or therapeutic target for the early stages of AD.

It is suggested that impairment to synaptic plasticity plays a crucial role in the development and progression of AD (Walsh and Selkoe, 2004; Shankar et al., 2008). According to Mecca et al. (2020) [^{11}C]UCB-J PET technology demonstrated significant synaptic loss caused by AD at neocortical areas such as frontal regions. Another study suggest that cerebellar LTP-like cortical plasticity mechanisms are impaired in AD (Di Lorenzo et al., 2020a). Since the discovery of SCD, neuropathological abnormalities in amyloidosis (e.g., reductions in Aβ42 and increases in amyloid tracer uptake) and neurodegeneration have appeared. The latter includes atrophy in the medial temporal lobes and paralimbic and temporoparietal cortices (Rabin et al., 2017). The loss of

Abbreviations: AD, Alzheimer's disease; AFT, Animal Fluency test; APB, abductor pollicis brevis; AVLT-DR, Auditory Verbal Learning Test-delayed recall; AVLT-H, Auditory Verbal Learning Test-Huashan version; AVLT-H-IR-S, AVLT-H immediate recall total score; AVLT-H-LR-S, AVLT-H long-term delayed recall score; AVLT-H-REC-S, AVLT-H recognition score; AVLT-H-SR-S, AVLT-H short-term delayed recall score; BNT-C, Boston Naming Test China version; DLPFC, dorsolateral prefrontal cortex; DST, digit span test; EMG, electromyography; EM, episodic memory; GLM, generalized linear model; iTBS, intermittent theta burst stimulation; ITT, intention-to-treat; LTP, long-term potentiation; MCI, mild cognitive impairment; MEP, motor evoked potential; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment Test; PFC, prefrontal cortex; RMT, resting motion threshold; rTMS, repetitive transcranial magnetic stimulation; SCD, subjective cognitive decline; SDMT, symbol digitized modality test; tDCS, transcranial direct current stimulation; TMT, trail making test; WMS-LM, Wechsler Memory Scale-Logical Memory Test.

long-term EM has not only been referred to as merely local damage to the medial temporal lobes, but also to the malfunction of cortical plasticity on the basis of memory processes (Vidal-Piñeiro et al., 2014). Considering the precocious impairment of plasticity mechanisms in AD, researching synaptic mechanisms in patients who show initial signs of memory deficits can effectively identify early functional anomalies, predict disease progression and evaluate the effectiveness of treatments. We, therefore, decided to study the change in LTP-like plasticity induced by SCD treatment with TMS.

The primary objective of our study is to investigate the efficacy of rTMS on EM in patients with SCD. The Auditory Verbal Learning Test-Huashan version (AVLT-H) will be used as the primary outcome measure. We also explore changes in the both neural and behavioral effects (other cognitive domains) after rTMS interventions. The predictive role of the LTP-like plasticity on cognitive improvement in rTMS-treated SCD patients will be studied. We hypothesized that stimulating the left-DLPFC (l-DLPFC) with 10 Hz rTMS can produce beneficial effects on EM in SCD by enhancing LTP-like plasticity.

2. Materials and methods

2.1. Study design

This is a randomized, double-blind, sham-controlled clinical trial, based on the Consolidated Standards of Reporting Trials (CONSORT) statement for non-pharmacologic therapy (Boutron et al., 2008). This study protocol was prepared in accordance with the Standard Protocol Items for Randomized Trials (SPIRIT) statement (Chan et al., 2015). The study was approved by the Human Research Ethics Committee at our hospital (No. 2023-002-01) and was registered with the Chinese Clinical Trial Registry (ChiCTR2300075517). **Figure 1** shows details of the study design. Baseline (T0) assessments will assess demographic, behavioral, neurophysiological, and neuroimaging indicators and, following completion of the intervention program (T1), instantaneous outcomes will be measured and compared between the two groups. Patients will undergo a comprehensive clinical investigation including a medical history and a thorough neuropsychiatric assessment exploring cognitive domains (e.g., global cognitive function, language function, executive function, memory, and attention), neuroelectrophysiological examination via TMS before and after completion of the procedure. Cognitive tests and TMS test will be performed in the morning and afternoon on the same day, respectively.

2.2. Participants

Enrollment of participants began in September 2023 from memory clinics, or surrounding communities. Right-handed participants will be screened and evaluated by a specialist using comprehensive neuropsychological test batteries at the Department of Rehabilitation Medicine of the Affiliated Jiangsu Shengze Hospital of Nanjing Medical University in China. All participants will sign a written informed consent before the program in accordance with the Declaration of Helsinki.

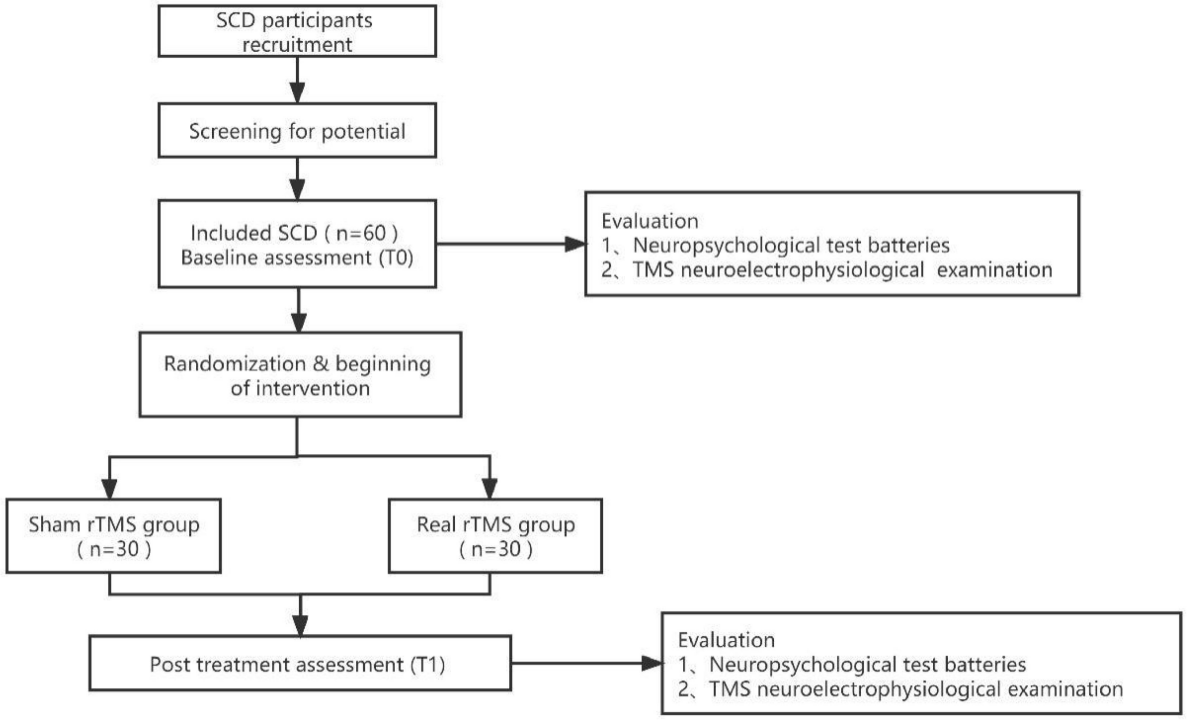

FIGURE 1
Study flow diagram.

2.3. Eligibility criteria

The inclusion criteria are based on Jessen's criteria as follows (Jessen et al., 2014; Shen et al., 2022): (1) not meeting the diagnosis of MCI on the standardized neuropsychological tests, including memory, speed/executive function, and language domains (Zhong et al., 2021); (2) self-perceived memory loss for at least 6 months; (3) presence of concern that performance in memory is worse than other people of the same age; (4) 55 to 80 years. The exclusion criteria are as follows: (1) clinical diagnosis of vascular dementia (Modified Hachinski Ischemic Score > 4) or dementia (NINDS-AIREN criteria); (2) drug or alcohol dependence within the last 6 months; (3) presence of severe cardiovascular or cerebrovascular disease or psychiatric disease; (4) contraindications to TMS; (5) treatment with antidepressants, anxiolytics, or central nervous system medications within 3 months prior to the assessments; (6) geriatric depression scale scores ≥ 6.

2.4. Sample size

According to Jia et al. (2021), the sample size was calculated using G*Power software, with a Cohen's effect size of $d = 0.7979$ for rTMS on the 12-word Philadelphia Verbal Learning Test as the primary outcome (Jia et al., 2021). Moreover, alpha and power are set at 0.05 and 80%, respectively. Our study will increase the inclusion number by 10% to compensate for possible patient shedding. The final number of participants will be 30 per group.

2.5. Randomization and blinding

The randomization procedure will be performed by a researcher at a 1:1 balanced distribution ratio of (real or sham group) using a web-based randomization tool.[1] Randomization information will be passed by sealed envelope until completion of the study. One investigator will oversee the random sequence and, at the intervention stage, the trained investigator will set the mode of the stimulus (real or sham group) according to the number on the paper in the envelope. Participants will be identified by codes rather than real names throughout the study. The neuroelectrophysiological assessor and the statistician will be blinded, as they are independently involved in the assessment or data analysis process, respectively.

2.6. Intervention

Repetitive transcranial magnetic stimulation (rTMS) treatment will be delivered using a D-MT500 magnetic biphasic stimulator (Neurosoft Ltd., Russia; peak magnetic field = 4T) equipped with an eight-shaped coil (AFEC-02-100-C; Neurosoft Ltd., Russia; diameter = 100 mm). Participants will randomly receive either rTMS or sham treatments over the l-DLPFC. The stimulation site is situated at the F3 point using the Bean F3 method as per the international 10–20 system for standardized placement of electroencephalogram (EEG) electrodes (Beam et al., 2009). Each treatment stimulation session consists of 10 Hz rTMS with 5 s train duration (50 pulses per train), and intertrain intervals of 10 s. In total, there are 40 trains with 2,000 pulses per day, 10 min each time, for 5 consecutive days per week for 4 weeks. Intensity will be set at 90% of the resting motion threshold (RMT) for each participant, defined as the minimum single-pulse intensity that triggers motor evoked potential (MEP) (not less than 50 μV) in at least 5 of 10 hotspots in the contralateral abductor pollicis brevis (APB) trial. The sham procedure is provided by the same device through a self-contained sham stimulus procedure. And the sessions are matched in all subjects.

The electromyography (EMG) system (Neuro-MEP-Micro, Russia) will be used to record the MEPs of the right-hand APB through surface Ag-AgCl electrodes. Through visual and EMG monitoring, entire relaxation of the muscle will be ensured. The coil is first placed on the left M1, and the handle placed backward at 45° against the midline of the sagittal plane of the brain. To determine the hotspot, where the lowest intensity induces the highest MEP amplitude, the coil is moved every 0.5 cm each time around the presumed scope. If the hotspot cannot be confirmed within 10 stimuli, the coil is shifted to the next location. Once the motor hotspot has been identified, the RMT will be determined.

2.7. Outcome measurements

2.7.1. Primary outcomes

The Auditory Verbal Learning Test-Huashan version (AVLT-H) assessment will be used as the primary outcome to assess EM for our study. The AVLT-H assesses several aspects of verbal EM through a list of 12 words, such as short or long-term delayed recall and recognition. It has been widely used as a semantic categorization memory test in mainland Chinese populations (Li et al., 2016). The AVLT-H scores include AVLT-H immediate recall total score (AVLT-H-IR-S), AVLT-H short-term delayed recall score (AVLT-H-SR-S) with a 5-min delay time, AVLT-H long-term delayed recall score (AVLT-H-LR-S) with a 20-min delay time, AVLT-H total, and AVLT-H recognition score (AVLT-H-REC-S) (Zhao et al., 2012). This test has been proved to be a sensitive diagnostic evaluation of cognitive impairment (Li et al., 2016).

2.7.2. Secondary outcomes

Other cognitive domain examinations and LTP-like cortical plasticity will also be measured. Overall cognitive function will be assessed using scores from the Montreal Cognitive Assessment Test (MOCA) as well as the Mini-Mental State Examination (MMSE). In addition, the Wechsler Memory Scale -Logical Memory Test (WMS-LM) and digit span test (DST) will be used to assess memory function and attention, respectively. Language function is measured using the scores of the Animal Fluency test (AFT) and Boston Naming Test China version (BNT-C) test. Measures of executive function include the symbol digitized modality test (SDMT) and the trail making test (TMT) parts A and B (Zhong et al., 2021). Time to completion of TMT A and TMT B will be logged and analyzed. In addition, all participants will be asked to complete two computer experiments conducted using E-Prime

1 http://www.randomization.com

2.0 software (Psychology Software Tools Inc., Pittsburgh, PA, United States). The n-back ($n = 1$) task is used to evaluate working memory, while the Go/No-Go task is used to assess inhibitory control ability (Borgwardt et al., 2008; Kumar et al., 2017). The accuracy and response time will be recorded.

The changes of the MEP amplitude will be measured to assess LTP-like cortical plasticity. Twenty consecutive MEPs of 5-s intervals will be evoked by single-pulse TMS at the left motor hotspot of 120% RMT intensity, and the peak-to-peak average value recorded. The whole LTP-like plasticity assessment includes five time points, whereby two baselines before and 5, 10, and 30 min after the intermittent theta burst stimulation (iTBS) protocol. Two baseline measurements are performed 10 min apart, and the subsequent iTBS paradigm is applied if the variation between the two average measurements is $< 15\%$. The iTBS protocol consists of a burst of three stimuli at 50 Hz and repeated at 5 Hz. A 2-s train of this protocol will be repeated every 10 s for a total of 192 s (600 pulses) with 80% RMT over the left hotspot (Huang et al., 2005; Yu et al., 2020).

2.8. Data analysis

SPSS V.23.0 will be used to analyze the data, and levels of statistical significance will be set at $p < 0.05$. For descriptive statistics, the Shapiro–Wilk test will be applied to check for normal probability prior to data entry. Data from the normal distribution will be reported as mean and standard deviation, whereas medians with interquartile ranges will be used to express the non-normal distribution. Categorical variables will be described as frequency as a function of percent. Demographic characteristics and baseline variables will be compared between the two groups using independent samples *t*-test or non-parametric Mann–Whitney test for continuous data, and comparisons of categorical variables using chi square or Fisher's exact tests. Based on the existing literature, we can determine whether the unbalanced baseline data affect the results and, if so, conduct covariance analysis using the baseline data as covariates to control for the effect of potential confounders. The experiment will be analyzed using intention-to-treat (ITT) and missing data will be interpolated using multiple imputation method.

For normally distributed data, a repeated-measures analysis of variance (ANOVA) will be conducted to evaluate changes in treatment effect between and within groups (group: real vs. sham rTMS) (time: pre-vs. post-treatment). Alternatively, for non-normally distributed variables, we will perform the Wilcoxon signed rank test for within group comparisons, and the Mann–Whitney test will be applied to compare the effect between groups at each time point. In addition, we also aim to use a repeated-measures ANOVA to examine LTP-like plasticity as a function of percent change at four time points (last baseline, 5, 10, and 30 min after iTBS) between the two groups. *Post hoc* comparisons between groups will be used using the Bonferroni correction method. The generalized linear model (GLM) will be considered if the data is not normally distributed. To investigate the relationship between brain measurements and clinical cognitive function characteristics, we will perform correlation analyses by repeated measures linear regressions.

2.9. Safety

Adverse events are any negative experiences, such as headache, vertigo, seizure, etc., that occur in a patient undergoing TMS. Any adverse event that happens during or immediately after stimulation by TMS should be reported. Participants will be screened strictly according to the inclusion and exclusion criteria to minimize the risk of adverse events. All adverse events will be recorded by the study staff on a case report form, primarily including the date, duration and severity. If a serious event occurs, it will be reported immediately to the principal investigator and the ethics committee. All participants were requested to complete TMSens_Q, a questionnaire designed to report unintended effects of rTMS at the end of every session (Giustiniani et al., 2022).

3. Discussion

We aim to assess the cognitive effect of 10 Hz rTMS stimulation specifically over the l-DLPFC. Markedly, non-drug interventions are more acceptable than pharmaceutical treatment for patients with milder symptoms of SCD. Current meta-analyses on traditional interventions (e.g., physical activity, education programs, and cognitive training) for SCD show that cognitive interventions have a modest effect in improving objective cognitive performance; however, in specific cognitive domains, the small improvements are still doubtful (Smart et al., 2017; Bhome et al., 2018). Therefore, we suggest that exploring a novel and promising treatment method such as TMS is of great value for the cognitive enhancement of SCD patients.

The DLPFC plays an essential role in governing EM binding and encoding robust representations (Wang et al., 2018). It is also the most prevalent and effective stimulation target to enhance cognitive function in MCI and AD (Zhang et al., 2022). The stimulation over this area may facilitate the top-down activation of semantic knowledge (Higo et al., 2011). This view agrees with some tDCS studies that show that the left superior parietal and the dorsolateral and anterior PFC regions are more intensely involved in the retrieval process of EM memory, and that stimulation over them facilitates verbal memory retrieval performance (Manenti et al., 2013; Vaqué-Alcázar et al., 2021). Turriziani et al. (2019) already found that the 1-Hz rTMS of the right DLPFC could improve EM performance compared to the sham rTMS and left DLPFC rTMS in AD patients. Accordingly, we decided to investigate whether the excitatory rTMS stimulation over the left DLPFC has the same promotion effect in our protocol. One study reported that higher activation was observed in the DLPFC of MCI subjects. The overactivity may represent a compensatory mechanism that allows these patients to perform better (Gigi et al., 2010). rTMS has the potential to recruit compensatory networks, such as the right prefrontal regions, which participate in memory coding processes (Solé-Padullés et al., 2006). High-frequency rTMS over the l-DLPFC could induce electrophysiological excitatory effects, and increase the efficiency of resource deployment in the prefrontal cortex (Li et al., 2017). For instance, 5 Hz rTMS has been proven to increase the locally successful correlated activity, like the local strength of PFC connectivity (Davis et al., 2017). Furthermore, some studies have found that the additional recruitment of neural

resources in the DLPFC region was considered to compensate for the reduction in hippocampal activation in SCD patient or hippocampus atrophy correlated with AD (Erk et al., 2011).

The cortical plasticity is thought to be an important mechanism for information processing in brain neural networks during motor and skill learning (Haley and Maffei, 2018; Mansvelder et al., 2019). LTP could also account for the neurophysiological basis of highly connected node formation. Based on the outcomes of our unpublished research, we have found that LTP-like cortical plasticity was significantly reduced in an SCD group when compared with an HC group. High-frequency rTMS can excite neurons directly, and correspondingly lower the threshold for synaptic transmission, making the synapse quite active and increasing synaptic connections. Potentially, high-frequency pulses of rTMS could generally induce LTP and restore cortical plasticity (Suppa et al., 2015). Li et al. (2021) reported that the cognitive improvement in patients with AD which correlated with changes in LTP was significant after 6 weeks of treatment with 20 Hz rTMS. However, few studies have yielded the effects of rTMS on LTP-like plasticity in SCD. Therefore, the present study will measure motor cortex plasticity as a proxy for the general form of cortical plasticity to examine the effect.

In this protocol, we assess other domains of cognitive function except for the EM. The small degree of progress in these domains also shows important clinical implications. The results of this trial may provide a significant improvement in cognitive deficits among SCD. Because the effective intervention at the SCD stage could increase the potential for disease reversal, it is particularly important to explore a feasible method thereof. If the results are positive, as expected, this study will shed light on a new direction in cognition management in SCD.

Ethics statement

The study was approved by the Human Research Ethics Committee of the Affiliated Jiangsu Shengze Hospital of Nanjing Medical University (No. 2023-002-01). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

TZ: Visualization, Writing–original draft. SH: Project administration, Writing–original draft. QL: Supervision, Writing–review and editing. JS: Writing–original draft. JT: Writing–original draft. TW: Conceptualization, Writing–review and editing. YS: Conceptualization, Funding acquisition, Methodology, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Neuromodulation of choice-induced preference changes: the tDCS study of cognitive dissonance

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Introduction: Difficult choices between two equally attractive options result in a cognitive discrepancy between dissonant cognitions such as preferences and actions often followed by a sense of psychological discomfort known as cognitive dissonance. It can lead to changes in the desirability of options: the chosen option becomes more desirable, whereas the rejected option is devalued. Despite the ample experimental evidence to show this effect, the neural mechanisms and timing of such choice-induced preference changes are not fully understood.

Methods: In this study, we used transcranial direct current stimulation (tDCS) to modulate the activity of the posterior medial frontal cortex (pMFC), which has been associated with conflict monitoring and choice-induced preference changes in neuroimaging studies. Prior to a revised version of Brehm's free-choice paradigm, participants in two experiments underwent cathodal (inhibitory) or anodal (excitatory) tDCS of the pMFC compared to sham (placebo) stimulation prior to the choice phase.

Results: Our results showed that cathodal tDCS significantly decreased the choice-induced preference change relative to a sham, but only in direct comparisons of rejected options. No significant effect of anodal tDCS in comparison with sham was observed.

Discussion: This study replicates the general behavioral effect of cognitive dissonance and provide partial support for the theory of the pMFC contribution to choice-related cognitive dissonance and subsequent preference changes, with possible limitations of an under-sampling for the obtained effect size and an asymmetry in the inhibitory-excitatory effects of non-invasive tDCS.

KEYWORDS

cognitive dissonance, decision making, preference changes, medial frontal cortex (MFC), transcranial direct current stimulation (tDCS), free choice paradigm

1 Introduction

Contrary to the assumptions of normative economic theory, choice preferences are not only driven by our attitudes but also modulated by the experience of previous choices. Brehm's study (1956) suggested that, after choosing between two similarly attractive options, individuals no longer perceive these options as similar, evaluating the chosen option more positively and devaluating the unchosen option. The devaluation of the rejected option has been repeatedly demonstrated in studies

using different versions of "free choice paradigm" (Kitayama et al., 2004; Izuma et al., 2010; Mengarelli et al., 2015; Colosio et al., 2017).

According to the prominent theory of cognitive dissonance (Festinger, 1957), "difficult" choices between similarly appealing options that require the rejection of one of them result in a cognitive discrepancy between dissonant cognitions such as preferences and actions. This discrepancy arises from the need to act in a manner that contradicts one's preferences and attitudes towards the highly favored option and may subsequently lead to a sense of psychological discomfort, also known as dissonance (Harmon-Jones and Mills, 2019). This discomfort motivates individuals to be consistent with their actions and reduce the dissonance by either devaluing the rejected option or increasing their evaluation for selected one. Thus, the mere act of choosing between similarly preferred options affects individual preferences.

In a typical "free choice paradigm," participants are asked to rate a set of goods according to their preference (*preference task I*). Next, they select between two of the items that had similar preference ratings in the first rating task (*choice task*). Finally, participants are asked to re-rate the original set of goods for the second time (*preference task II*). According to the theory of cognitive dissonance, after making a difficult choice between two equally preferred items, participants' preference, guided by the need to resolve conflict, can decrease for the rejected item and increase for the chosen ones. The resulting difference between the assessment of the items in *preference task II* and *preference task I* could represent the observable resolution of cognitive dissonance: spreading of alternatives or choice-induced preference changes. Alteration of preference was observed in plenty of studies, either preference devaluation for rejected options (for example, Izuma and Murayama, 2013; Salti et al., 2014; Colosio et al., 2017) or an increase in evaluation for selected ones (for example, Sharot et al., 2010; Izuma and Murayama, 2013).

Importantly, the free-choice paradigm can produce artificial preference changes (see Chen and Risen, 2010; Izuma and Murayama, 2013; Enisman et al., 2021 for a review). Chen and Risen (2010) showed that measured alteration in preference when making a difficult decision may not necessarily be associated with the choice itself; rather, it may be a result of the artifact, while choice and repeated evaluation merely uncover already existing preferences. For example, preference for *option 1*, measured by rating or ranking, can slightly exceed preference for *option 2*, although the ratings were equal during *preference task I*. Therefore, it is likely that in *preference task II*, preference rating for *option 1* will continue to get even higher, producing ostensible changes of preference. To counter this drawback of the "free-choice paradigm," various control conditions and task modifications have been suggested and investigated (Chen and Risen, 2010; Izuma and Murayama, 2013; Enisman et al., 2021). The use of the brain stimulation approach also may overcome the limitations of the free-choice paradigm. Alterations in preference in making difficult conflictual decisions under region-specific brain stimulation may be attributed to the suppression or enhancement of the neuronal activity in the region responsible for conflict monitoring and resolution, and cannot be attributed to a statistical artifact. Therefore, the substantial effect of well-controlled brain stimulation on the following conflictual decision spreading of alternatives is likely attributable solely to the modulation of neural mechanisms underlying choice-induced preference changes.

Despite the significant progress in studying cognitive dissonance, neurocognitive mechanisms of preference alteration in decision making are still not fully understood. Several studies consistently indicated the involvement of the pMFC (van Veen et al., 2009; Izuma et al., 2010), posterior cingulate cortex (Kitayama et al., 2013; Tompson et al., 2016), dorsolateral prefrontal cortex (Harmon-Jones et al., 2008; Flavia Mengarelli et al., 2015), and nucleus accumbens (Izuma et al., 2010; Kitayama et al., 2013) to post-decisional preference changes. The involvement of other brain regions was not replicated. It is likely these brain regions form a network responsible for detection dissonance and its subsequent resolution (Colosio et al., 2018; Voigt, 2022).

A growing number of studies indicate the critical role of the posterior medial frontal cortex (pMFC) in cognitive dissonance and preference re-evaluation (van Veen et al., 2009; Izuma et al., 2010; Colosio et al., 2017; Voigt et al., 2019; Tandetnik et al., 2021). This part of the brain largely consists of the pre-supplementary motor area (pre-SMA), the dorsal medial frontal cortex (dmPFC), ventral medial frontal cortex (Voigt et al., 2019), and the dorsal anterior cingulate cortex (dACC) (Izuma, 2013; Tandetnik et al., 2021). A number of fMRI studies consistently showed activations in Brodmann areas 10/24/32 in both left and right hemispheres (Izuma, 2013). The pMFC has been associated with monitoring of conflicts, cognitive control, error detection (Carter et al., 1998; Botvinick et al., 1999, 2001; Holroyd Nieuwenhuis et al., 2003; Danielmeier et al., 2011), and reward-based decision making (Williams et al., 2004). Overall, pMFC activity has been linked to performance monitoring and behavior adjustment. Recently, neuroimaging studies have focused on the role of the pMFC in cognitive dissonance and following the difficult choice preference changes (van Veen et al., 2009; Izuma et al., 2010; Jarcho et al., 2011; Kitayama et al., 2013; Voigt et al., 2019). A multichannel electroencephalographic (EEG) study demonstrated that the fronto-central resting state activity predicted the individual strength of preference changes and the magnitude of the dissonance-related neural activity (Colosio et al., 2017). The newest fMRI study showed partitioning of the activity of the medial frontal cortex: vmPFC is associated with expected reward-based decision making, whereas dmPFC is linked with metacognitive aspects of decisions such as deliberation and confidence about the alternatives and choice (Clairis and Pessiglione, 2022). Thus, the activity of the medial frontal cortices at rest affects different aspects of the behavioral effects of cognitive dissonance.

The use of a neuromodulatory approach with the help of repetitive transcranial magnetic stimulation (rTMS) (Izuma et al., 2015) facilitated the unveiling of the causal role of the pMFC in generating and reducing cognitive dissonance in a modified "free-choice paradigm" with a "choice-blindness" procedure. A disruption of pMFC activity, using 1 Hz rTMS right after the choice stage of the free-choice paradigm, significantly reduced the choice-induced preference changes. Although the rTMS approach demonstrated great potential in elucidating the causal relationship between cortical areas, the temporal aspect of the rTMS precludes one from understanding whether choice-induced preference changes take place during *preference task II* or the *choice task*. In the past decade, functional neuroimaging studies (e.g., Izuma et al., 2010) have explored the neural underpinning of cognitive dissonance, predominantly during the post-decisional stage of the "free choice paradigm" when subjects rated options again, some time after making difficult choices (Izuma and Murayama, 2013). This is based on the theoretical proposition that cognitive dissonance is experienced after making a difficult

decision, which subsequently leads to an increase in preference for the chosen highly attractive option and a decrease in preference for the rejected one. Importantly, the activity of the pMFC was demonstrated already during the making of such a decision (*choice task*) (Kitayama et al., 2013; Voigt et al., 2019), which supports the hypothesis about the occurrence of preference changes while making a choice. An EEG study with use of "free choice paradigm" demonstrated that difficult decisions during the choice task are associated with stronger evoked elevated activity in the pMFC, reflected in a larger fronto-central error-related negativity (ERN) response, compared to easy decisions (Colosio et al., 2017). A comparison of ERN amplitude between trials featuring difficult and easy choices revealed that the ERN amplitude was higher for difficult ones. Furthermore, the ERN amplitude correlated with the magnitude of choice-induced preference changes. The difference waves (trials in difficult choices versus trials in easy choices) in Cz electrodes position significantly correlated with the extent of spread of alternatives. Thus, a stronger ERN was observed in the Choice task, and the stronger individual preferences were later altered for rejected items in Preference task II (Colosio et al., 2017). Since ERN activity was manifested during choices, the above-mentioned results suggest that the pMFC may be involved in the preference changes at an earlier stage than previously thought. This hypothesis about alteration of preference at an early stage is also supported by the studies of metacognitive aspects of choices (Lee and Daunizeau, 2020; Lee and Holyoak, 2021; Clairis and Pessiglione, 2022).

In this study, we applied transcranial direct current stimulation (tDCS) over the pMFC to probe the critical role of the pMFC in choice-induced preference changes and its contribution to cognitive dissonance during decision-making. The tDCS is a non-invasive neuromodulation technique that temporarily enhances (more often, anodal stimulation) or reduces (more often, cathodal stimulation) cortical excitability. This effect is achieved through applying a constant weak electrical current through an electrode placed on the surface of the scalp. Importantly, tDCS may result in facilitation of, or interference with the targeted brain region activity underlying changes of behavior (Nitsche and Paulus, 2001; Nitsche et al., 2008; Brunoni et al., 2012). This technique has been recently employed to explore the role of the medial frontal cortex in the modulation of error processing and performance monitoring (i.e., the modulation of the ERN and feedback-related negativity) in both clinical (Reinhart et al., 2015) and healthy populations (Bellaïche et al., 2013; Reinhart and Woodman, 2014). Here, we have conducted two sham-controlled experiments with delivering cathodal tDCS of the pMFC (Experiment 1) and anodal tDCS of the pMFC (Experiment 2). Using tDCS, we do not anticipate any effect of brain stimulation on ostensible preference changes due to statistical artifact found by Chen and Risen (2010) for *option 1* and *option 2*. Therefore, any significant differences in preference changes across stimulation conditions could be predominantly attributed to the causal role of the pMFC in evoked by difficult choices spread of alternatives.

By applying tDCS at the preliminary decision stage of the "free choice paradigm," we expected to exert control on the cortical excitability of the pMFC, and thus observe either a reduction (after cathodal stimulation) or an increase (after anodal stimulation) of the choice-induced preference changes compared to the non-stimulated (sham tDCS) condition, particularly after making difficult choices. The previous study by Colosio et al. (2017) demonstrated more explicit and accurately interpreted alteration of preference after hard choices specifically for the options which were rejected. Therefore, to specify hypothesis and test the stimulation effect, in this study, we were mainly interested in the alteration of preference for rejected option under tDCS, expecting a decrease in the devaluation of the attitude towards declined options in difficult decisions.

2 Materials and methods

2.1 Participants

Two groups of healthy right-handed volunteers were invited to participate in one of two experiments. Taking into consideration a little knowledge about neuromodulatory effects on the activity of the pMFC using the non-invasive tDCS in the cognitive dissonance theory, we took an averaged group number (17–20 participants) based on the studies with similar design. For the experiment with cathodal tDCS stimulation (Experiment 1), we recruited 18 volunteers. One of them was excluded due to a distraction during the experiment, leaving 17 participants in total (mean age = 22.15, 9 males). For the experiment with anodal tDCS (Experiment 2), we recorded the data of 24 participants. We excluded five participants from the analysis due to the following reasons: (1) one participant had a technical problem with the software; (2) another participant experienced highly uncomfortable sensations from tDCS; (3) three participants reported strong fatigue. Thus, for Experiment 2, we analyzed the results of 19 participants (mean age = 23 years, 9 males).

All participants were instructed to fast at least 3 h before each session. All participants were naïve to tDCS and the nature of the experiment; they were not informed about the protocol received (i.e., sham or stimulation). Participants were recruited through posted advertisements and participated in this experiment in exchange for a small monetary compensation (equivalent to ~10 USD). All volunteers had a normal or corrected-to-normal vision and took no regular medications. None of the subjects had a history of neurological or psychiatric illness. The study protocol was approved by the Institutional Review Board of the HSE of the National Research University Higher School of Economics (Statement of Opinion on compliance of the Empirical Research Project with ethical norm). All participants gave informed written consent before entering the study.

2.2 Transcranial direct current stimulation procedure

Each participant received both an active and sham stimulation in two different experimental sessions. Within each group, participants were randomly assigned to receive either tDCS (cathodal tDCS in Experiment 1 or anodal tDCS in Experiment 2) or control (sham) stimulation during the first session, whereas the remaining stimulation was delivered during the second session a week later. The tDCS protocols were based on the safety guidelines (Antal et al., 2017).

The tDCS was applied using a battery-driven 8-channel constant current neuro-stimulator (Startstim 8, Neuroelectrics) and two conductive rubber electrodes hosted in saline-soaked synthetic sponges (active

electrode, 19.25 cm^2; reference, 52 cm^2). The active electrode was placed over the medial-frontal cortex (FCz position of the international EEG 10–20 system) and held in place by a neoprene headcap, while the reference electrode was placed diagonally at the center of the right cheek.

For active stimulation, the current was increased over the first 30 s. Then cathodal or anodal direct current was delivered constantly for 20 min at an intensity of 1.5 mA. This protocol has been successfully used to down-regulate the medial frontal cortex and associated ERN component (see Reinhart and Woodman, 2014, for details of the current flow model). The impedance was controlled by *Neuroelectrics Instrument Controller* software v1.4, (NIC, Neuroelectrics) and was kept below 10 kΩ. After 20 min of stimulation, the current was ramped down over 30 s. The sham tDCS stimulation was administered following the same procedure as the active tDCS stimulation, but stimulation lasted only 30 s, ramping up and down at the beginning and the end of the 20 min period, producing the same tingling sensations associated with active stimulation. Such a sham stimulation protocol has been shown to be a reliable control condition in both naïve and experienced participants (Gandiga et al., 2006).

2.3 Stimuli

Two sets of 223 digital (sets A or B), colorful photos of snack foods on a white background (chocolate, chips, small fruit or vegetable, cheese, etc.) were used as stimuli. We counterbalanced sets A and B across stimulation conditions. To ensure that both sets of stimuli contained similarly attractive items, we used ratings provided by 45 participants (20 males, mean age of 22.17) during our previous experiment (see Colosio et al., 2017, for details) to determine the average preference of each item. Then we assigned items to set A or B in such a way that both sets would consist of the same number of items, and item ratings would show similar distributions and standard deviations (see the results section for statistics).

The photos were projected onto a screen with a visual angle of 4.772° vertically and 7.62° horizontally.

2.4 Experimental design

Participants underwent a modified version of Brehm's free-choice paradigms (Brehm, 1956) in the stimulation and sham sessions. The basic free-choice paradigm consisted of three main parts: (1) *preference task I*, (2) *choice task*, and (3) *preference task II*. Figure 1 illustrates the overall experimental design.

During *preference task I*, participants rated a set of 223 food items on an 8-point Likert scale (1 = "I do not like it at all" to 8 = "I like it a lot"). Each item was presented at the center of the screen for 3 s. The tDCS montage was set up, and active/sham tDCS was administered right after the end of *preference task I* and lasted for 20 min, during which, participants were instructed to sit comfortably on a chair.

During the *choice task*, each trial was formed by a pair of food items presented on the screen for 5 s. The trials were either *self*-choices, when participants make a decision themselves, or control *computer* choices, when participants had just to confirm the choice made by computer. In these choices, participants were not responsible for the choice and had not to experience dissonance. In *self-trials*, participants were instructed to select the preferred item by pressing the corresponding button on a computer keyboard. To enhance a participant's motivation to select preferred items, participants were informed that they would receive one of the chosen items along with a show-up fee at the end of the experiment. The composition of each trial and the number of pairs in the choices were determined by the individual's ratings of the items during the first *preference task I*. Participants were unaware that a computational algorithm used individual ratings to create the *self-trials*. Thus, we modulated choice difficulty by creating *self-difficult trials* that evoked high cognitive dissonance, as pairs were formed by highly preferred food items (rated between 6 and 8) and *self-easy trials*, which evoked low cognitive dissonance, since the pairs were formed by a highly preferred item and a poorly rated one (rated below 3). In the control *computer trials*, participants were instructed to press the button corresponding to the item which was randomly selected by the computer (highlighted by a red square). The *computer trials* were formed using the same criterion used to create *self-difficult trials*. All items were used only once during the *choice task*. At the beginning of each trial, participants were informed about the trial type ("your choice" or "computer choice"). Participants had 5 s to either choose an item or press the keyboard button corresponding to the computer's choice. If there was no answer, a written message prompted participants to respond faster. Pairs in each choice condition were selected based on the participants' ratings, thus the number of probes varied per person. On average, it reached 25 trials for difficult choices, 25 trials for easy choices, and 27 trials for computer choices.

During *preference task II*, participants rated the same set of food items. The only difference from *preference task I was an* additional message for items involved in the choice task. To be consistent with the previous studies (Izuma et al., 2010; Izuma and Murayama, 2013; Colosio et al., 2017) and to reduce the chance of participants forgetting their choice and to maximize the potential dissonance, these items were presented with a message informing the participant about which choice had been made (accepted or rejected item, e.g., "You rejected it"), either by the participant or the computer.

Finally, participants attended an additional control condition, namely a *post-ex (post-experimental) choice*. This task was introduced by Chen and Risen (2010) and was used in the work of Izuma et al. (2010) for control confounding preference changes. Chen and Risen noticed that re-evaluation of items could occur without the choice, followed by cognitive dissonance. In *post-ex* choice trials, as in *computer* trials in the *Choice* task, items were selected using the same criteria as in self-difficult trials. However, items, picked up for this *post-experimental* choice, were not assigned to any *self-choice* during the choice task. So, for these items, the order was "rate-rate-choose" instead of "rate-choose-rate" which eliminates confounding re-evaluations.

At the end of the experiment, we randomly selected one of the items that participants had selected during *self-difficult* trials or *post-ex* choice trials as an additional reward for the participants.

2.5 Statistical analysis

To evaluate how preferences were altered in decision-making, we compared the difference in items evaluation (ratings) between pre-choice *preference task I* and post-choice *preference task II* across different choice and stimulation types. The stimulation conditions comprised either active real stimulation (*cathodal tDCS* in Experiment 1 or *anodal tDCS* in Experiment 2) or *sham* (placebo stimulation).

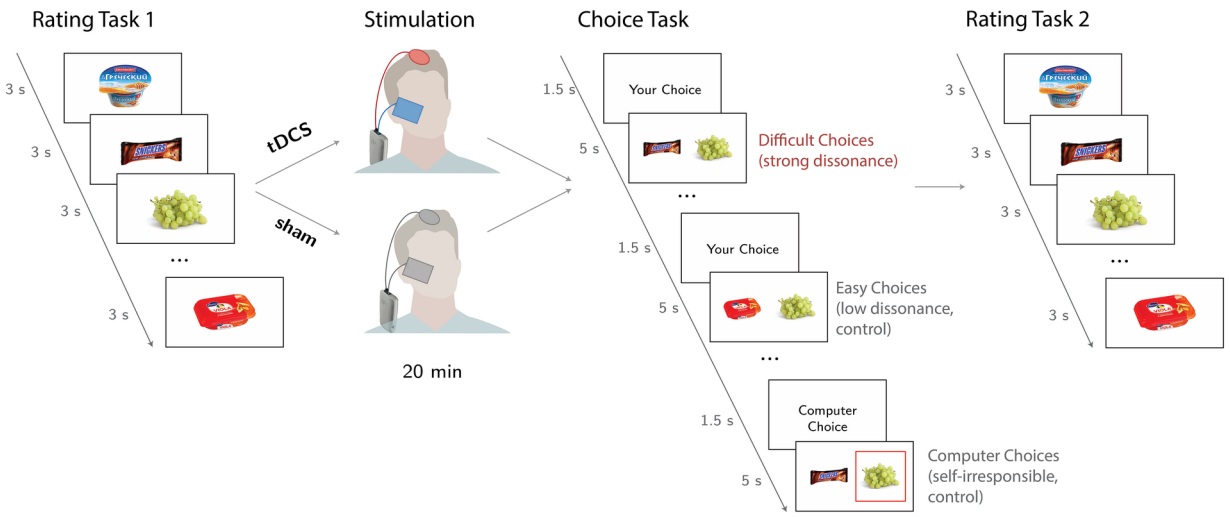

FIGURE 1
"Free-choice paradigm" used in the study. During preference task I (Rating task 1), participants rated food items presented on the screen for three seconds. Next, during the Choice Task, subjects freely selected one of two food items (self-difficult trials evoked strong cognitive dissonance, while self-easy trials evoked weak cognitive dissonance). In the computer trials, subjects chose the item that was selected by the computed algorithm, which was highlighted by a red square. In preference task II (Rating task 2), participants rated the same food items again.

Types of choices (trials) included *difficult*, *easy*, and *post-experimental self-choices*, and *computer* choices. Choice types involved *rejection* or *selection* of items during the all types of choices. The mean of choice-induced preference changes served as the dependent variable and measured as the preference (rating) of the item in *preference task II* minus the preference (rating) of the same item in *preference task I*.

We aimed at modulating the re-evaluation process while making difficult self-choices under tDCS of the pMFC. We reasoned as follows: if the stimulation had an effect, then for items rejected in difficult self-choices, one would expect the decrease in preference changes under cathodal (inhibitory) tDCS (Experiment 1), and the increase in preference changes under anodal (excitatory) tDCS (Experiment 2) for the same kind of items, respectively, in comparison with sham stimulation. We also expected to observe the main effect of cognitive dissonance, i.e., stronger preference changes for items rejected during *self-difficult* choices (in general and separately in the target tDCS trials) as compared to selected ones and to items rejected in easy and computer choices (and no *post-ex* choices), which served as control conditions.

The main research hypothesis was to probe the modulatory effect of tDCS on preference changes (to reduce preference changes in Experiment 1 or to increase preference changes in Experiment 2). Taking into account the multiple-factor structure, the alteration of preference was only interesting when certain conditions were combined. The key point involved the comparison of mean choice-induced preference changes for items *rejected* in the *self-difficult* trials in the *tDCS* condition vs. those in the *sham* condition, using paired *t*-tests separately in each experiment. For the test of the general effect of cognitive dissonance, three separate paired t-tests were also performed. The tests compared mean preference changes in the tDCS condition for items *rejected* in the *self-difficult* trials vs.: (1) items *selected* in the *self-difficult trials*; (2) items rejected in the *self-easy trials*; (3) items rejected in the *computer trials*. All *t*-tests were performed with Bonferonni correction (alpha corrected = 0.05/4 = 0.0125). To assess whether changes in preference could reveal pre-existing preference rather than being associated with choice, we performed two-way 2 × 2 repeated measures ANOVA with two withing-subject factors: Choice (*rejected* or *selected*) and *Paradigm* (RCR, "rate-choice-rate" with *self-difficult* or *self-easy* choices), and RRC ("rate-rate-choice," with *computer* and *post-ex choices*).

Next, for deeper investigation of the general effect of the tDCS on choice-induced preference changes, we performed the analysis of the mean preference changes for all the data obtained from both rejected and selected items using the linear mixed effects models (LME) (Bates et al., 2015a). In order to take into account individual differences, *Subject* was taken as a random factor, whereas *Stimulation* (cathodal tDCS vs. sham stimulation in Experiment 1 and anodal tDCS vs. sham stimulation in Experiment 2), *Trial type* (*self-difficult*, *self-easy*, *computer*) and Choice type (selected item vs. rejected item) were included as fixed factors. Post-experimental trials were not included here.

Data preprocessing and analysis was performed with R (R Core Team, 2022) in RStudio RStudio (RRID:SCR_000432) using R packages 'data.table' (Dowle and Srinivasan, 2019), 'ez' (Lawrence, 2016; RRID:SCR_020990), 'lme4' (Bates et al., 2015b; RRID:SCR_015654) 'effsize' (Torchiano, 2020), and 'pwr' (Champely, 2020). Visualizations were performed using the 'ggplot2' package (Wickham, 2016; RRID:SCR_014601). R-scripts for analysis and datasets are available on OSF.[1]

2.6 Linear mixed-effects model selection

The initial model design was chosen according to the principle of maximization random factor structure where all possible effects of random factors are considered using random intercepts and random

1 https://osf.io/abpqj

slopes for the influence of all fixed factors (Barr et al., 2013). Estimation of maximal models, however, may not converge (Bates et al., 2015a). Taking into account the increased probability of getting type I error for random-intercepts-only models in within-subjects experimental design (Barr et al., 2013), the highest priority was given for models with both a random intercept and a random slope for at least one parameter. Further decisions about including random intercepts and random slopes for different fixed factors and goodness of fit of the model were made according to the model selection conditional Akaike Information Criterion (cAIC). cAIC provides special correction of estimation uncertainty of the random effects variance parameters based on a numerical approximation (Säfken et al., 2018). For coefficient estimates, the restricted maximum likelihood method (REML) was used instead of the maximum likelihood (MLE), which provides better computation in case of unbalanced design and unknown variance of random factors. It allows compare models with the same fixed factor and different random factors.

In both Experiment 1 and Experiment 2 cAIC showed the lowest (the best) value for the following model with correlated random intercept and slope, which has the structure Preference changes ~ Stimulation × Trial type × Choice type + (Stimulation|Subject). In a simplified form this model has formula:

$$\begin{aligned} &PC_{si} = \beta_0 + S_{0s} + (\beta_1 + S_{1s})\,\text{Stimulation}_i \\ &+ \beta_2\,\text{Type}_i + \beta_3\,\text{Choice}_i + \beta_4\,\text{Stimulation}_i \\ &\times \text{Type}_i + \beta_5\,\text{Stimulation}_i \times \text{Choice}_i \\ &+ \beta_6\,\text{Type}_i \times \text{Choice}_i + \beta_7\,\text{Stimulation}_i \\ &\times \text{Type}_i \times \text{Choice}_i + \varepsilon_{si}; \\ &\varepsilon_{si} \sim N\left(0;\sigma^2\right) \end{aligned}$$

where $\beta_0 - \beta_3$ – coefficients for intercept and slopes for fixed factors, $\beta_4 - \beta_7$ – coefficients for slopes for fixed factors interaction, S_{0s} and S_{1s} – coefficients for intercept and slope for random factor *Subject*.

Additional information regarding model selection is provided in Supplementary Material.

3 Results

The comparison of preferences for food items in A and B sets in pre-study proved that the sets had similar mean ratings (Set A = 4.70 ± 0.87; Set B = 4.69 ± 0.88). The independent *t*-test showed no significant difference between preferences for food items in sets A and B: $t_{(222)} = 0.06$, $p = 0.94$. The Shapiro–Wilk test for normality ensured that set A ($W = 0.991$, $p = 0.215$) and set B ($W = 0.990$, $p = 0.121$) were sampled from normal distribution.

3.1 Experiment 1. Effect of cathodal tDCS of the pMFC on choice-induced preference changes

Paired *t*-test demonstrated that mean changes in preference for items rejected in self-difficult choices under cathodal tDCS were smaller than after sham condition ($t(16) = -3.29$, $p = 0.002$, Cohen's $d = 0.28$, Hedges's $g = 0.27$, one-sided). Figure 2 illustrates the result (the first two bars on the barplot), which confirmed our hypothesis: in self-difficult trials, cathodal tDCS significantly reduces choice-induced preference changes for rejected items compared to the placebo condition.

Preferences for *self-difficult* trials for the *rejected* items were significantly devalued comparatively to the *selected* ones ($t(33) = -7.85$, $p < 0.001$, Cohen's $d = 1.08$, one-sided), which supports the general effect of cognitive dissonance. We also observed the significant difference between choice-induced preference changes for *rejected* items in target *self-difficult* trials and control *self-easy* trials ($t(33) = -7.65.83$, $p < 0.001$, Cohen's $d = 1.41$, one-sided) and for *rejected* items in target *self-difficult* and control *computer* trials ($t(33) = -3.33$, $p = 0.001$, Cohen's $d = 0.57$, one-sided). All these comparisons are shown in Figure 2. Two-way repeated measures 2 × 2 ANOVA Choice × Paradigm showed significant influence on preference changes for both factors Choice ($F(1, 16) = 10.14$, $p = 0.006$, $\eta^2 p = 0.05$) and Paradigm ($F(1, 16) = 13.37$, $p = 0.002$, $\eta^2 p = 0.07$), whereas interaction of Choice × Paradigm was insignificant ($p = 0.22$).

LME analysis (marginal $R^2_m = 0.25$, conditional $R^2_c = 0.55$) revealed significant contribution to preference changes on the subjects level of *Trial type* ($F(2, 160) = 26.51$, $p < 0.001$, $\eta^2_p = 0.25$), Choice type ($F(1, 160) = 8.58$, $p = 0.004$, $\eta^2_p = 0.05$), and their interaction of Trial type × Choice type ($F(2, 160) = 22.57$, $p < 0.001$, $\eta^2_p = 0.22$). Other factors and interactions were not significant, including the target *Stimulation* factor ($p = 0.23$) and interaction of Stimulation type × Trial type × Choice type ($p = 0.66$). Coefficients estimates are provided in Table 1. ANOVA output on the LME model is shown in the Table 2. Descriptive statistics for mean choice-induced preference changes for items rejected in self-difficult choices under cathodal tDCS and sham are provided in the Supplementary Table S1.

3.2 Experiment 2: effect of anodal tDCS of the pMFC on choice-induced preference changes

Unlike Experiment 1, the paired *t*-test comparing preference changes for rejected in self-difficult choices items under anodal tDCS and sham stimulation did not reveal significant difference ($p = 0.15$). This result is illustrated by the left side of Figure 3 (the first two bars on the barplot).

As expected for having general cognitive dissonance effect, preference changes in *self-difficult* trials were significantly down for *rejected* items than for *selected* ones ($t(37) = -11.73$, $p < 0.001$, Cohen's $d = 2.08$, one-sided). Also preferences changes for *rejected* items in *self-difficult* trials were significantly stronger than in *self-easy* ($t(37) = -11.62$, $p < 0.001$, Cohen's $d = 2.05$) and *computer* trials ($t(37) = -8.13$, $p < 0.001$, Cohen's $d = 1.23$). These comparisons are summarized and shown in Figure 3. Two-way repeated measures 2 × 2 ANOVA Choice × Paradigm showed significant influence on preference changes for both factors Choice ($F(1, 18) = 30.24$, $p < 0.001$, $\eta^2 p = 0.34$) and Paradigm ($F(1, 18) = 6.15$, $p = 0.023$, $\eta^2 p = 0.03$), whereas interaction of Choice × Paradigm was not significant ($p = 0.67$).

LME analysis (marginal $R^2_m = 0.4$, conditional $R^2_c = 0.55$) revealed significant contribution to preference changes on the subjects level of factors *Trial type* ($F(2, 180) = 35.28$, $p < 0.001$, $\eta^2_p = 0.28$), *Choice type* ($F(1, 180) = 32.23$, $p < 0.001$, $\eta^2_p = 0.15$), and their interaction Trial type × Choice type ($F(2, 180) = 47.33$, $p < 0.001$, $\eta^2_p = 0.34$). Other

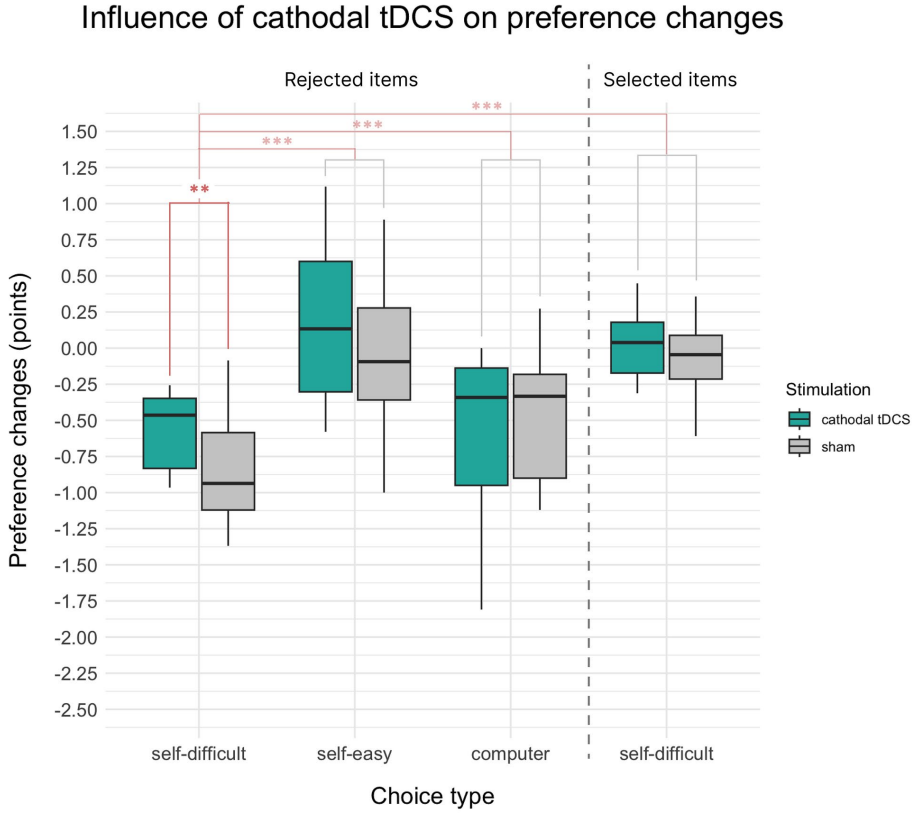

FIGURE 2
Mean choice-induced preference changes in Experiment 1 after cathodal tDCS or sham, indexed in points on an 8-point Likert scale. Target alteration of preference for items rejected in self-difficult choices under cathodal tDCS was smaller than after the sham condition (the median being closer to zero). The control comparisons of preference changes for items rejected in self-difficult choices were also significantly different from items selected in self-difficult choices and from items rejected in self-easy and computer choices. Significance level is indicated: $p < 0.001$ as ***, $p < 0.01$ as **, and $p < 0.05$ as *.

factors and interactions were also not significant, including the factor *Stimulation* ($p = 0.1$) and interaction of Stimulation type × Trial type × Choice type ($p = 0.5$). Table 2 provides the results of the LME analysis. Coefficients estimates are provided in Table 3. ANOVA output on the LME model is shown in the Table 4. Descriptive statistics for mean choice-induced preference changes for items rejected in self-difficult choices under cathodal tDCS and sham are provided in the Supplementary Table S2.

The main results of two experiments and comparison of effect of cathodal and anodal tDCS in both experiments with its sham groups are summarized and illustrated in Supplementary Figure S1. Interpretation of comparison these results can be complicated due to individual differences between participants of studies: independent *t*-test showed no statistically significant difference in choice-induced preference changes in the *self-difficult* trials between anodal and cathodal stimulation in Experiment 1 and Experiment 2.

4 Discussion

In the current study, we used cathodal and anodal tDCS of the pMFC right before the *choice task* of the "free choice paradigm" to investigate the neural mechanism of the cognitive dissonance and subsequent choice-induced preference changes.

Regardless of the stimulation, we replicated a general behavioral effect of cognitive dissonance in both experiments: the preferences for items rejected in *self-difficult* (conflictual) choices significantly decreased after making the choice, compared to *self-easy* (non-conflictual) and computer (self-irresponsible) choices. This effect was observed regardless of the type of non-invasive tDCS: preference re-evaluation was detected in both Experiment 1 with inhibitory (cathodal) tDCS and Experiment 2 with excitatory (anodal) tDCS.

In Experiment 1, we observed that cathodal (inhibitory) tDCS of the pMFC particularly diminished choice-induced preference changes on declined options in difficult choices compared to the sham stimulation. This result supported the causal role of the pMFC in preference changes while making a difficult choice: suppressing the activity of the pMFC by cathodal tDCS prior to the choice reduced the reevaluation of the preference for rejected options. However, this result was demonstrated only in direct comparison using t-test, and effect size of the stimulation was comparatively small (Cohen's $d = 0.28$). Further investigation of the general influence of cathodal tDCS on preference re-evaluation using linear mixed effects models (LME) did not show the significant effect of the tDCS.

In Experiment 2, we found no significant effect of anodal tDCS of the pMFC on the preference changes: neither in a focused analysis of the rejected items in *self-difficult* trials in comparison with sham condition nor analyzing data using linear mixed effect model.

TABLE 1 Experiment 1. Coefficient estimates of LME model with fixed factors stimulation, trial type, choice type, and random factor subject with correlated random intercept and random slope for stimulation.

Predictors	Estimates	CI	*p*
(Intercept)	−0.51	−0.81–−0.21	**0.001**
Stimulation_cathodal	−0.04	−0.37–0.28	0.812
Type_self-difficult	−0.58	−0.88–−0.27	**<0.001**
Type_self-easy	0.49	0.18–0.79	**0.005**
Choice_selected	−0.09	−0.39–0.22	0.607
Stimulation_cathodal × Type_self-difficult	0.29	−0.14–0.72	0.229
Stimulation_cathodal × Type_self-easy	0.26	−0.17–0.69	0.288
Stimulation_cathodal × Choice_selected	0.05	−0.38–0.48	0.844
Type_self-difficult × Choice_selected	1.07	0.64–1.50	**<0.001**
Type_self-easy × Choice_selected	−0.00	−0.43–0.43	0.997
Stimulation_Cathodal × Type_self-difficult × Choice_selected	−0.29	−0.90–0.32	0.394
Stimulation_Cathodal × Type_self-easy × Choice_selected	−0.24	−0.85–0.37	0.479

TABLE 2 Experiment 1. Results of ANOVA on LME model for choice-induced preference changes.

Fixed factor	Sum Sq	Mean Sq	Num Df	Den Df	*F*	*p*	η^2_p
Stimulation	0.1	0.1	1	16	0.47	0.5	
Trial type	15	5	3	224	24.34	<0.001***	0.25
Choice type	3.65	3.65	1	224	14.7	<0.001***	0.07
Stimulation × Trial type	0.34	0.11	3	224	0.55	0.65	
Stimulation × Choice type	0.21	0.21	1	224	1	0.31	
Trial type × Choice type	11.32	3.77	3	224	18.3	<0.001***	0.2
Stimulation × Trial type × Choice type	0.22	0.07	3	224	0.36	0.78	

LME model included fixed factors stimulation (cathodal tDCS vs. sham) × Trial type (difficult vs. easy vs. computer) and the choice type (rejected vs. selected) and random factor subject with correlated random intercept and random slope for stimulation. Significance level is indicated: $p < 0.001$ as ***, $p < 0.01$ as **, and $p < 0.05$ as *.

One of the main possible reasons for not finding the strong effect of stimulation in two experiments as we expected is high probability of getting a false negative result. Having a limited knowledge of the neuromodulatory effects of tDCS on the activity of the pMFC in the cognitive dissonance studies poses difficulties to a prior calculation of the appropriate sample size in order to obtain reliable result. The posterior calculation of the statistical power, based on the observed effect size in Experiment 1, did not reach 80%, which makes a false negative outcome highly likely. Descriptive statistics (Supplementary Tables S1, S2) for choice-induced preference changes under stimulation and without it showed substantial heterogeneity and variability. We invited participants without neurological and psychiatric diseases and the use of any medication asked them not to drink coffee and alcohol on the day of the experiment and excluded those who experienced extreme fatigue and discomfort during the experiment. More attention should undoubtedly be paid to controlling the participants' states in tDCS-experiments, due to the severe variability in the stimulation effect. These results can be used in subsequent tDCS-studies for prior calculation of the required sample size based on the statistical power and enhance the experimental design.

Another explanation of the current outcome in Experiment 2 is asymmetry in inhibitory-excitatory effects of non-invasive tDCS. This is supported by the results of a number of previous studies that have demonstrated heterogeneity of anodal and cathodal stimulation (Fregni et al., 2005; Karim et al., 2010; Mengarelli et al., 2015; for a meta-analysis see Jacobson et al., 2012). Some studies have specifically reported that there was no significant behavioral modulatory effect of anodal tDCS (Karim et al., 2010; Fagerlund et al., 2015; Conley et al., 2016). Further tDCS studies of conflict monitoring and resolution are needed to reconcile the asymmetry in stimulation effects and, in particular, to differentiate between the influence of anodal stimulation. Subsequent tDCS studies of choice-induced preference changes should pay specific attention to searching for the optimal target of brain stimulation. For example, evidence suggests that the more anterior subregions of the pMFC (FPz site) did not result in any modulatory effect on the ERN (Bellaïche et al., 2013). Systematic calculating of the electric field across many studies or the use of the high-definition tDCS could also be beneficial in reconciling the tDCS results across studies.

One further debatable point is the potential compensation of the effect of tDCS of the pMFC by the activity of unaffected brain areas, such as the dorsolateral prefrontal cortex (DLPFC). Recent investigations provide further evidence that a whole brain network is involved in the process of preference changes (Colosio et al., 2018; Voigt, 2022). For example, neuroimaging studies indicated an

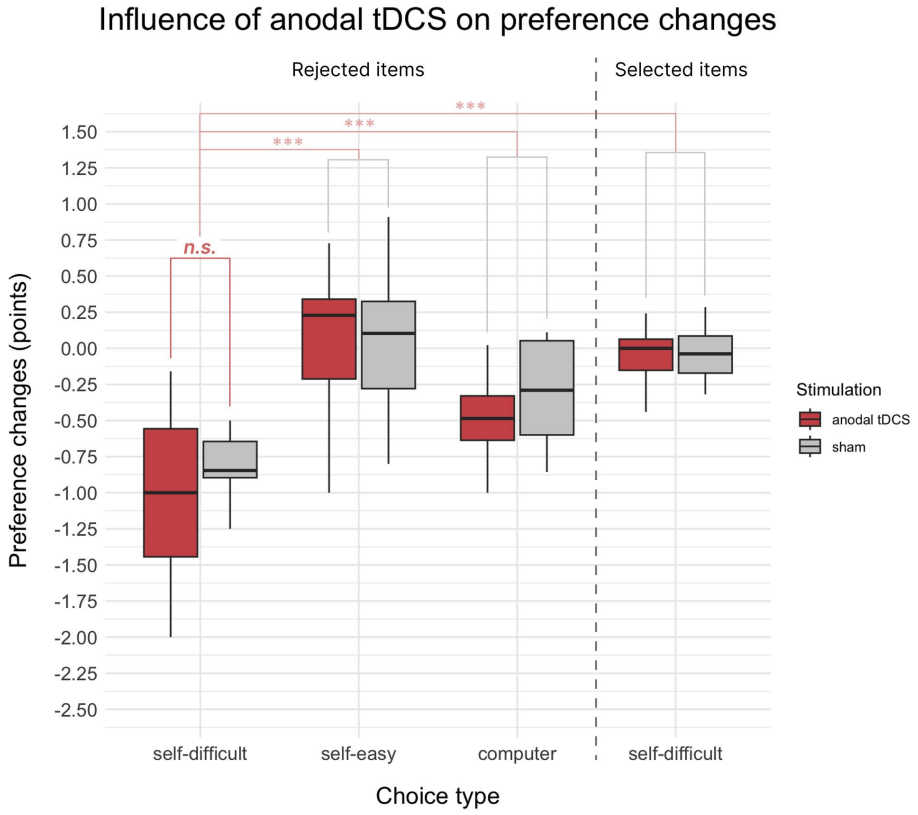

FIGURE 3
Mean choice-induced preference changes in Experiment 2 after anodal tDCS or sham, indexed in points on an 8-point Likert scale. Target alteration of preference for items rejected in *self-difficult* choices under anodal tDCS did not show a significant difference from the sham condition. The control comparisons of preference changes for items rejected in self-difficult choices were significantly different from items selected in self-difficult choices and from items rejected in self-easy and computer choices. Significance level is indicated: $p < 0.001$ as ***, $p < 0.01$ as **, and $p < 0.05$ as *.

important role for the DLPFC in cognitive dissonance (Harmon-Jones and Harmon-Jones, 2008; Harmon-Jones et al., 2011; Mengarelli et al., 2015). Mengarelli et al. (2015) down-regulated the DLPFC by a 15 min, 1 mA cathodal tDCS. Offline stimulation of the left DLPFC significantly reduced the post-decision preference changes, and hence suggested that the left DLPFC plays an important role in the behavioral effects of cognitive dissonance. The role of the DLPFC in choice-induced preference changes is still under discussion, but it is thought to contribute to more general cognitive control mechanisms, regardless of whether conflicts is present (Harmon-Jones et al., 2011; Izuma et al., 2015). Interestingly, Ridderinkhof et al. (2004) proposed the existence of a functional pMFC-DLPFC network which supervises performance monitoring and executions. Further studies should focus on the development of possible controls for electromagnetic stimulation which can elucidate the interaction between the pMFC and DLPFC in choice-induced preference changes.

Although many neuroimaging studies demonstrated that the pMFC plays a central role in conflict monitoring, cognitive control and conflict resolution, little is certain about the chronometry of neuronal mechanisms of choice-induced preference changes. One of the first studies to show fMRI signatures of cognitive dissonance at the post-decisional stages in a "free choice paradigm" demonstrated that more conflicted decisions were associated with the larger pMFC activity during *preference task II*, compared to less conflicted decisions (Izuma et al., 2010). Of note, the majority of previous literature studying cognitive dissonance and choice-induced preference changes in the 'free choice paradigm," focused on the neural activity after decision during *preference task II* (Izuma and Murayama, 2013). For example, TMS of the posterior medial frontal cortex (pMFC) decreased preference changes only if applied at the later stages of the paradigm – right before *preference task II* (Izuma et al., 2015). However, relation between the pMFC and post-decisional preference changes is not always supported by experimental finding. For example, Kitayama et al. (2013) also showed elevated activity of the pMFC during making difficult conflictual choices (compared to easy ones), but found no correlation between the activity of the pMFC and post-decisional attitude changes. The neuroimaging study of Jarcho et al. (2011) examined the decisional phase of the decision-based cognitive dissonance paradigm and observed increased activity of the pMFC regions during the decision but not after it. Voigt et al. (2019) demonstrated, using fMRI and eye tracking, that activity of the DLPFC and pMFC, as well as and fixation duration during the making of hard decisions, predicted the magnitude of subsequent preference changes. Our study supports this evidence. Importantly, the duration of the tDCS after-effect is still a matter of debate: some studies have reported that a 20 min, 1.5 mA stimulation could generate a modulatory effect for several hours (Nitsche and Paulus, 2001; Nitsche et al., 2003; Reinhart and Woodman, 2014). In that case, in our study,

TABLE 3 Experiment 2. Coefficient estimates of LME model with fixed factors stimulation, trial type, choice type, and random factor subject with correlated random intercept and random slope for stimulation.

Predictors	Estimates	CI	*p*
(Intercept)	−0.30	−0.47–−0.14	**<0.001**
Stimulation_anodal	−0.23	−0.46–0.01	0.055
Type_self-difficult	−0.60	−0.80–−0.40	**<0.001**
Type_self-easy	0.34	0.14–0.54	**0.003**
Choice_selected	0.02	−0.18–0.22	0.865
Stimulation_anodal × Type_self-difficult	0.09	−0.19–0.38	0.571
Stimulation_anodal × Type_self-easy	0.20	−0.09–0.48	0.214
Stimulation_anodal × Choice_selected	0.11	−0.17–0.40	0.479
Type_self-difficult × Choice_selected	0.83	0.55–1.12	**<0.001**
Type_self-easy × Choice_Selected	−0.13	−0.41–0.16	0.432
Stimulation_anodal × Type_self-difficult × Choice_selected	−0.05	−0.46–0.35	0.817
Stimulation_anodal × Type_self-easy × Choice_selected	−0.24	−0.64–0.16	0.287

TABLE 4 Experiment 2. Results of ANOVA on LME model for choice-induced preference changes.

Fixed factor	Sum Sq	Mean Sq	Num Df	Den Df	*F*	*p*	η^2_p
Stimulation	0.35	0.35	1	18	3.47	0.08	
Trial type	8.83	2.94	3	252	29.34	<0.001***	0.25
Choice type	10.47	10.47	1	252	104.37	<0.001***	0.07
Stimulation type × Trial type	0.08	0.02	3	252	0.25	0.86	
Stimulation type × Choice type	0.02	0.02	1	252	0.17	0.68	
Trial type × Choice type	14.21	4.7	3	252	47.24	<0.001***	0.2
Stimulation type × Trial type × Choice type	0.16	0.05	3	252	0.55	0.65	

Here and below, LME model included fixed factors stimulation (cathodal tDCS vs. sham) × Trial type (difficult vs. easy vs. computer) and the Choice type (rejected vs. selected) and random factor Subject with correlated random intercept and random slope for Stimulation. Significance level is indicated: $p < 0.001$ as ***, $p < 0.01$ as**, and $p < 0.05$ as *.

cathodal tDCS could inhibit cortical activity during both the *choice task* and *preference task II*. Thus, new protocols should be developed to differentiate neural activity of the DLPFC and pMFC in the mechanisms of choice-induced preference changes.

Another interesting question is about the metacognitive aspects of preference changes in decision making. Some studies showed that at least partially preference changes can be attributed not to the fact of making difficult choices or the necessity of rearranging preferences to resolve conflicts, but rather to the internal refinement of the choice based on the certainty of pre-choice value judgment and confidence about the options in the decision (Lee and Daunizeau, 2020; Clairis and Pessiglione, 2022). Lee and colleagues provided a computational model for the online metacognitive control of decisions (Lee and Daunizeau, 2021; Lee et al., 2023). The fMRI study showed that value-based decision making and metacognitive evaluation of the option can be separated even at the neuronal levels (Clairis and Pessiglione, 2022). Therefore, it is important in future studies of the preference changing in making difficult decisions to disentangle the effects of the choice when comparing the expected values of the options and the subjective metacognitive process regarding this choice.

Generally, we traced the neuromodulatory (inhibitory) effect of cathodal tDCS on choice-induced preference changes. This effect was consistent with the proposed role and temporal dynamics of the pMFC: inhibiting the pMFC through cathodal tDCS, a key region in conflict detection and behavioral adjustments, prior to the making of a difficult decision, decreases the preference changes. This effect, however, was rather small, manifested only in direct comparisons with placebo stimulation and showed an asymmetry to the anodal (excitatory) tDCS, which did not demonstrate an increase in preference changes.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found here: https://osf.io/abpqj.

Ethics statement

The studies involving humans were approved by Institutional Review Board of the National Research University Higher School of Economics. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ER: design of the study, data collection for experiment 2, statistical data analysis for experiment 1 and experiment 2, writing all sections of the manuscript, and figures and tables creation. MC: conceptualization and design of the study, stimuli development, and data collection for experiment 1. AS and VK: supervising the study and revision the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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The effect of bipolar bihemispheric tDCS on executive function and working memory abilities

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Introduction: Cognitive functioning is central to the ability to learn, problem solve, remember, and use information in a rapid and accurate manner and cognitive abilities are fundamental for communication, autonomy, and quality of life. Transcranial electric stimulation (tES) is a very promising tool shown to improve various motor and cognitive functions. When applied as a direct current stimulus (transcranial direct current stimulation; tDCS) over the dorsolateral pre-frontal cortex (DLPFC), this form of neurostimulation has mixed results regarding its ability to slow cognitive deterioration and potentially enhance cognitive functioning, requiring further investigation. This study set out to comprehensively investigate the effect that anodal and cathodal bipolar bihemispheric tDCS have on executive function and working memory abilities.

Methods: 72 healthy young adults were recruited, and each participant was randomly allocated to either a control group (CON), a placebo group (SHAM) or one of two neurostimulation groups (Anodal; A-STIM and Cathodal; C-STIM). All participants undertook cognitive tests (Stroop & N Back) before and after a 30-minute stimulation/ sham/ control protocol.

Results: Overall, our results add further evidence that tDCS may not be as efficacious for enhancing cognitive functioning as it has been shown to be for enhancing motor learning when applied over M1. We also provide evidence that the effect of neurostimulation on cognitive functioning may be moderated by sex, with males demonstrating a benefit from both anodal and cathodal stimulation when considering performance on simple attention trial types within the Stroop task.

Discussion: Considering this finding, we propose a new avenue for tDCS research, that the potential that sex may moderate the efficacy of neurostimulation on cognitive functioning.

KEYWORDS

transcranial direct cortical stimulation (tDCS), executive functions, working memory (WM), left dorsolateral prefrontal cortex (DLPFC), neuromodulation

Introduction

Cognitive functioning is central to the ability to learn, problem solve, remember, and use information in a rapid and accurate manner (Morley et al., 2015). Fiocco and Yaffe (2010) highlighted that cognitive abilities are fundamental for communication, autonomy, and quality of life. It has been well established that those who experience cognitive impairment show a decreased ability to execute daily living activities, and are at increased risk of

mortality, compared to those with no cognitive impairment (Johnson et al., 2007). Two fundamental aspects of cognition are executive functioning (EF) and working memory (WM) (Timmann and Daum, 2007). EF involves the ability to focus attention, plan and attend to task-relevant information in a 'noisy' environment (Dubreuil-Vall et al., 2019). Borghini et al. (2018) emphasized the importance EF has on cognitive functioning, and explain that a key attribute of EF is the ability to ignore task-irrelevant information and maintain focus of attention. In conjunction with EF, working memory (WM) refers to the system that maintains newly acquired information in the mind for rapid retrieval while performing complex tasks such as reasoning, comprehension and learning (Fregni et al., 2005; Baddeley, 2010; Logie, 2011; Grot et al., 2017; Al Qasem et al., 2022).

To evaluate performance of EF and WM among individuals, two well established tasks administered within the literature are the Stroop Task (Stroop, 1935) and N-Back letter (Kirchner, 1958) task respectively. The Stroop task tests the ability to shift one's attention (Spreen and Strauss, 1998) in the presence of distraction, or, alternatively to suppress irrelevant information and maintain attentional focus. It is believed to provide a measure of cognitive inhibition (Boone et al., 1990; Archibald and Kerns, 1999). Alternatively, the N-Back task, presents participants with a continual stream of stimuli at fixed intervals, and participants must determine whether each stimulus matches the one presented 'N' items before. An advantage of the test is that processing load can be varied systematically by manipulating the value of N, which alters both accuracy and reaction time (RT) (Jonides et al., 1997).

The importance of WM and EF can be readily observed among individuals suffering deficits in these cognitive abilities. For example, both WM and EF deficits are among the most common symptoms associated with Alzheimer's disease (AD) (Stopford et al., 2012). In addition to AD, deterioration in EF and WM performance has been associated with numerous neurological and mental disorders, including schizophrenia, attention-deficit/hyperactivity disorder (ADHD), major depressive disorder (MDD), bipolar affective disorder, mild cognitive impairment (MCI), post-traumatic stress disorder, traumatic brain injury, epilepsy, and neurodegenerative dementia and movement disorders (Stegmayer et al., 2015; Maehler and Schuchardt, 2016; Grot et al., 2017; Le et al., 2017; Dubreuil-Vall et al., 2019). Finally, aging is associated with deficits in WM which reduce one's ability to process and maintain task-irrelevant information (Pelosi et al., 2000; Gruber et al., 2011; Le et al., 2017). Due to the impact that WM and EF deficits have on independence and quality of life as one ages or experiences disease, significant research attention has been allocated toward improving these cognitive abilities in clinical (Li et al., 2021), aging (Giuli et al., 2016) and in young healthy populations (Schmiedek et al., 2014). One tool that has emerged as a promising candidate for augmenting cognitive abilities in these populations is neurostimulation.

Among a variety of neurostimulation techniques that currently exist, transcranial electric stimulation is a promising tool shown to improve various motor (Abdelmoula et al., 2016; Angius et al., 2016; Saruco et al., 2017; Toth et al., 2019) and cognitive (Antal et al., 2001, 2004; Kwon et al., 2008; Sparing et al., 2009; Fregni et al., 2015) functions. Most commonly applied as a direct current stimulus (transcranial direct current stimulation; tDCS), this form of neurostimulation has been shown to slow cognitive deterioration (Murugaraja et al., 2017) and potentially enhance cognitive functioning (Javadi and Walsh, 2012; Dubreuil-Vall et al., 2019; Figeys et al., 2021), particularly when applied over the dorso-lateral pre-frontal cortex. tDCS is a non-invasive brain stimulation approach which applies a weak current ~1–2mA over a target region of the cortex to affect the excitability of the underlying neurons. Typically, anodal stimulation involves the depolarization of cortical neurons, thus increasing cortical excitability (Kwon et al., 2008). Cathodal stimulation is understood to have the opposite effect, decreasing cortical excitability (Thair et al., 2017). However, this knowledge largely stems from work investigating the impact of tDCS on motor networks. When used to probe regions predominantly involved in cognitive functioning, results are less clear, with some studies finding positive cathodal effects with no anode effects (Jacobson et al., 2012).

Considering the effects of tDCS specifically on EF and WM abilities, limited work exists among young healthy adults, with some concluding that anodal tDCS over the left DLPFC can enhance WM, with no effect of cathodal stimulation (Fregni et al., 2005; Baumert et al., 2020). Alternatively, anodal stimulation of the left posterior parietal lobe has been shown to worsen working memory performance (Talsma et al., 2017). For EF, conclusions are also mixed with some studies claiming improvements in response inhibition (Loftus et al., 2015; Friehs et al., 2021) while others suggest stimulation leads to increased impulsivity (Shen et al., 2016). While many tDCS studies have discussed targeting the left DLPFC, the right DLPFC remains largely unexamined with little evidence that this area might be involved in working memory (Wu et al., 2014). Moreover, most tDCS paradigms have primarily involved monopolar stimulation of the left DLPFC as opposed to bipolar, bihemispheric monatages. In a study by Waters et al. (2017), they demonstrate the role of the ipsilateral hemisphere has in motor tasks and highlight the increased efficacy of bihemispheric compared to unipolar stimulation. This presents an opportunity as little work has examined the effect of bipolar DLPFC tDCS on EF and WM performance to date.

The purpose of this study is to test whether bihemispheric tDCS over the left DLPFC can improve WM and EF abilities in young adults, evaluated using the N-Back letter and Stroop tasks respectively. We first hypothesize that sensitivity on the N-Back task, and response times and accuracy on the Stroop task, will improve between pre and post stimulation attempts for control (no tDCS) and placebo (sham tDCS) groups. Secondly, we hypothesize that those receiving bihemispheric tDCS with the anode placed over the left DLPFC will show performance improvements on N-Back and Stroop tasks over and above those observed for control and sham groups. Finally, we hypothesize that those receiving bihemispheric tDCS with the anode placed over the right DLPFC will show blunted performance improvements between pre and post N-Back and Stroop tasks compared to those observed for control and sham groups.

Methods

Participants

A total of 72 healthy young adults [36 female; age 22.97 ± 3.44 years (mean ± SD)] with no neurological disorders provided informed written consent prior to participating in the study. Participants were instructed to refrain from alcohol 24 h prior and caffeine 6 h prior to participation in the study. Each participant was randomly allocated to one of four groups such that nine male and nine female participants were allocated to each group: a control group (CON), a placebo group (SHAM) and two neurostimulation groups (a-STIM and c-STIM; described below). The study was approved by the university research ethics committee in accordance with the declaration of Helsinki.

Cognitive tasks

Inquisit 5 software (Millisecond Software LLC) was used to administer Stroop and N-Back Letter tasks and collect data regarding participant performance.

Stroop task

The Stroop task has been extensively adopted for neuropsychological testing (Scarpina and Tagini, 2017). During the task, participants were presented with one of 4 words ("red," "green," "black," or "blue") or a colored rectangle (in one of the same 4 colors) on a white background. Words were also presented in red, green, black, or blue colored font. Stimuli were categorized into three different trial types. Congruent trials contained words written in the same color font (i.e., "blue" presented in blue font). Incongruent trials contained color words written in a font of a different color (i.e., "blue" presented in green font). Control trials were those containing colored rectangles. Participants responded to a total of 84 trials during the task with seven trials involving each of the four colors within each trial type. Participants were instructed to always respond to the font color and not the word, as accurately and quickly as possible. Participants pressed the keys on the keyboard "d," "f," "j," and "k" which corresponded respectively to the answers red, green, blue and black. The key bindings were represented at the top of the screen in gray ink throughout the duration of the task. Errors and response times (RT; in milliseconds) were recorded for each trial.

N-Back letter task

The N-Back Letter task used in this study was adapted to include 0-back, 1-back and the 2-back blocks (3-back excluded). During each block of the task, participants were presented with a stream of the following consonants in white font on a black screen, one after the other: B, C, D, F, G, H, J, K, L, M, N, P, Q, R, S, T, V, W, Y, Z. Each letter was presented on the screen for 500 ms, the screen then remained blank for 3000 ms until the next stimulus showed.

During the 0-Back block, the first consonant presented was the target letter and participants had to remember this one letter and indicate every time this letter appeared in the sequence of presented letters by pressing the "A" key on the keyboard. For the 1-Back block, participants were asked to press the "A" key if the current letter presented was the same as the letter shown previously in the sequence. For the 2-Back block participants were asked to press the "A" key if the current letter presented was the same as the letter presented two letters before. The participants completed a short practice sequence of each block once and then completed 3 test sequences of each block presented in order of difficulty (0-Back → 1-Back → 2-Back). We recorded the number of hits (correct recognition of the target letter), correct rejections (correct recognition of a non-target letter), misses (failed recognition of a target letter), and false alarms (indicating falsely that a non-target letter was a target letter).

Transcranial direct current stimulation

Two identical bespoke neurostimulation devices designed by Flow Neuroscience (Flow^{TM}) (https://www.flowneuroscience.com) were used to administer 2mA of bihemispheric tDCS to the DLPFC of participants in the A-STIM and C-STIM groups. Those in the A-STIM group used the device with the anode and cathode over the left and right DLPFC respectively. Alternatively, those in the C-STIM group used the device with the anode and cathode reversed, that is, over the right and left DLPFC respectively. Saline sponges were fixed to two 22.9 cm^2 spheric electrodes (current density = 0.09 mA/cm^2) and current was delivered for 30 min. Those participants in the SHAM group wore the same headset as the A-STIM participants, however, the current was only increased to only 1mA and then back to 0mA over two 30s intervals, and then remained off for the remainder of the 30 min intervention. Finally, those participants in the CON group wore the headset but it was never turned on. To maintain a similar cognitive engagement of participants across groups (Toth et al., 2019), all participants during the 30 min played tetris.

Protocol

Participants began by providing demographic information, including their age, sex, color blindness, and concussion history. Any participants who were color-blind or had had a concussion in the last 5 years were excluded from participating (no participants excluded). Following this, participants completed the Brunel Mood Scale Questionnaire (BRUMS), to assess their current mood state. Following completion of the BRUMS, each participant performed baseline attempts of the Stroop and the N-Back tasks. The order of presentation of the two tasks was randomized for each participant. Following the baseline attempt at both cognitive tests, participants completed the 30-min neurostimulation intervention according to their group allocation (CON, SHAM, A-STIM, C-STIM). After completing the intervention phase of the protocol, participants completed the BRUMS a second time as well as a post test of the Stroop and N-Back Letter tasks in the same order as they

did at baseline. Finally, after completing the experiment, each participant indicated whether they believed they had received neurostimulation during the 30-min intervention.

Data processing

For each trial type of the Stroop task (Control, Congruent, Incongruent) RTs within baseline or post tests were averaged across like trials to provide an average RT for each participant. Errors were counted to calculate the % of trials participants correctly responded to for a given trial type (Percent Correct).

For the N-Back Task, 1-Back and 2-Back Hits, Misses, Correct Rejections and False Alarms were used to calculate sensitivity on these blocks of the task (D-Prime; d'). D-Prime was calculated as the difference between the z transforms of the hit and false alarm rates [d' = z (Hit Rate) – z (FA rate)] (Macmillan and Creelman, 1990). The hit rate was calculated as [hits/(hits + misses)]. Where the hit rate was 1, an adjusted hit rate was calculated (n-0.5)/n, where n refers to the number of target trials (for the task used in this study, the number of target trials across three iterations of a given block was 15). The False Alarm rate was calculated as false alarms/(false alarms + correct negative). Where the false alarm rate was 0, an adjusted false alarm rate was calculated as (0.5/n) where n refers to the number of non-target trials (for the task used in this study, the number of non-target trials across three iterations of a given block was 30).

Data analysis

Data analyses were performed using SPSS version 28. Normality of data residuals were assessed through observing Shapiro-Wilk statistics and histogram plots and heterogeneity of variance was assessed using a Levene's test. Where variance heterogeneity was violated, Greenhouse-Geisser corrections were applied. Where *post-hoc* comparisons were made, Sidak alpha adjustments were applied.

To assess the hypothesis that sensitivity on the N-Back task, and response times and accuracy on the Stroop task, would improve between pre and post stimulation attempts for control (no tDCS) and placebo (sham tDCS) groups, we performed separate paired samples *t*-tests comparing baseline and post test scores for each group.

To assess the hypothesis that anodal and cathodal stimulation would respectively improve and disimprove Stroop and N-Back task performance compared to those in the control and placebo (sham) conditions, we performed 2-way (Sex by Condition) ANCOVAs, with baseline scores inputted as a covariate in the model.

Finally, we conducted 3-way (Sex by Condition by Session) ANOVAs on each of the 8 mood categories assessed through the BRUMS questionnaire. We note that the inclusion of sex in the above two models was predicated on the ability to recruit equal numbers of males and female participants and effects examined were exploratory.

TABLE 1 Paired *t*-tests analysis of practice effects for Stroop and N-Back tasks.

Task	Metric	Stimulus type	Baseline vs. Post (*p*-value)
Stroop	Accuracy (Percent Correct)	Control	0.544
		Congruent	**0.029**
		Incongruent	**<0.001**
	Response Time (RT; ms)	Control	**<0.001**
		Congruent	**<0.001**
		Incongruent	**<0.001**
N-Back	Sensitivity (D-Prime; d')	1-Back	0.927
		2-Back	**0.003**

Bold values denote statistical significance $p < 0.05$.

Results

Practice effect

Paired *t*-tests revealed a practice effect for all measures of the Stroop task except Accuracy (percent correct) on Control trials (Table 1). It also revealed a practice effect for performance on the 2-Back, but not 1-Back, block of the N-Back task (Table 1).

Neurostimulation effect

For Stroop task metrics, a significant main effect of Condition was observed for Accuracy on congruent trials [$F_{(3,69)} = 3.783$, $p = 0.015$, [[Mathtype-mtef1-eqn-1.mtf]]$\eta_p^2 = 0.157$) as was a significant interaction between sex and condition [$F_{(3,69)} = 3.628$, $p = 0.018$, $\eta_p^2 = 0.151$]. *Post-hoc* analysis showed that for Male participants, accuracy on post test congruent trials was significantly greater following both anodal and cathodal stimulation when compared to those receiving no stimulation (Control) or a sham stimulation (placebo) (ASTIM-Control $p < 0.001$; ASTIM-Sham $p = 0.008$; CSTIM-Control $p = 0.001$; CSTIM-Sham $p = 0.02$) (see Figure 1). No significant main effect of Sex, Condition or interaction effect was found for any other Stroop task metric (Table 2).

For N-Back task metrics, no significant main effect of sex, Condition or interaction effect was found for either 1-Back or 2-Back performance (Table 2). A trend was observed however, suggesting post test performance improvements on the 2-Back were blunted by the anodal stimulation (Figure 1).

When observing results from each of the 3-way ANOVAs on the 8 moods captured by the BRUMS questionnaire, we noticed a significant effect of Time for Tension [$F_{(1,62)} = 22.882$, $p < 0.001$, $\eta_p^2 = 0.27$], Confusion [$F_{(1,62)} = 5.489$, $p = 0.022$, $\eta_p^2 = 0.081$] and

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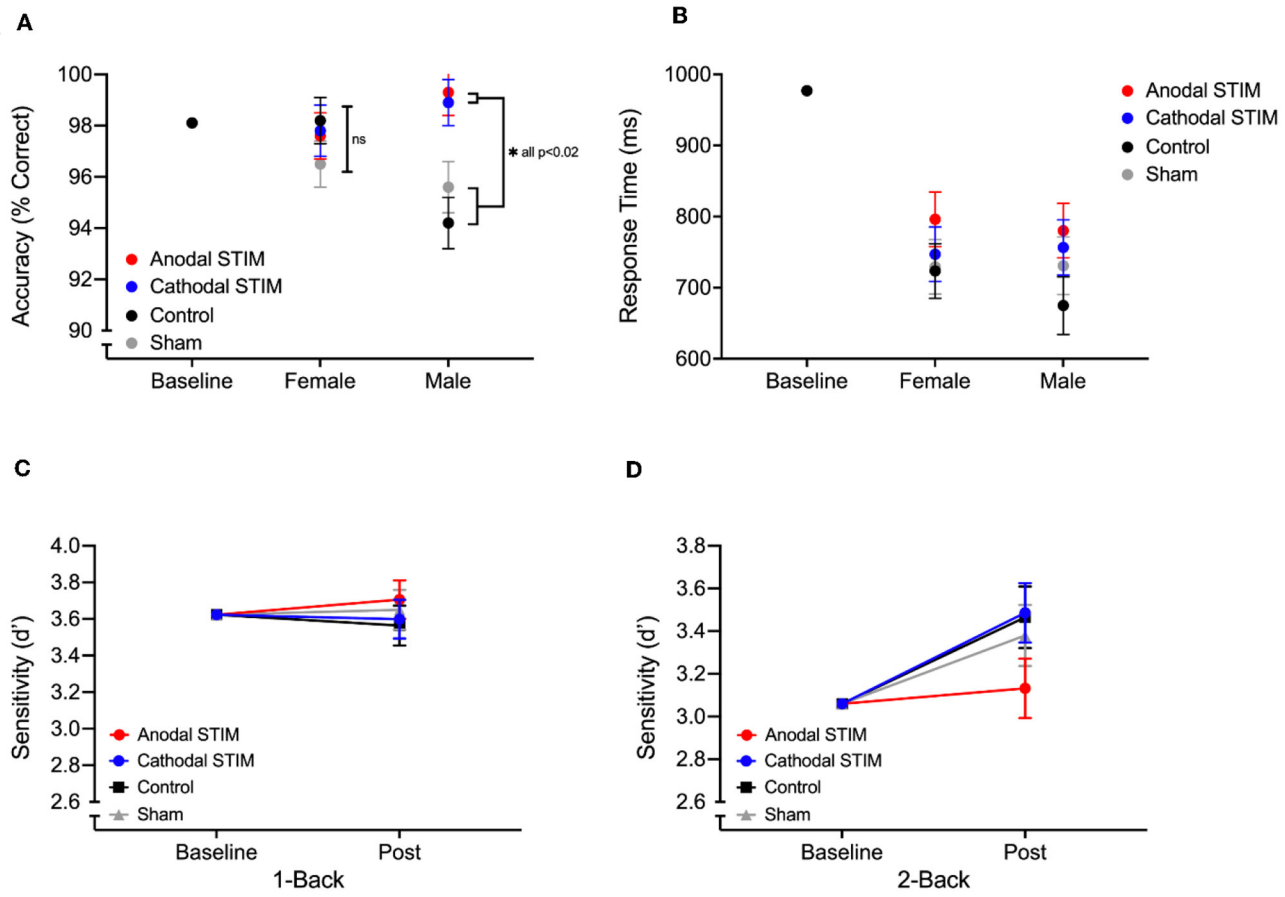

FIGURE 1
Post test stroop accuracy **(A)** and response times **(B)** on congruent trials of the Stroop task by male and female participants in each of the 4 stimulation groups. ANCOVA adjusted means are displayed with standard errors with covariate baseline score represented with the black circle. **(C, D)** show adjusted means of sensitivity on Post test 1-Back and 2-Back levels of the N-Back task, with covariate baseline scores.

calmness [$F_{(1,62)} = 8.272$, $p = 0.006$, $\eta_p^2 = 0.118$], demonstrating all participants overall were less tense, confused, and calm at post test compared to baseline. We also observed a main effect of condition for vigor [$F_{(1,62)} = 5.489$, $p = 0.022$, $\eta_p^2 = 0.081$], happiness [$F_{(1,62)} = 5.489$, $p = 0.022$, $\eta_p^2 = 0.081$] and calmness [$F_{(1,62)} = 5.489$, $p = 0.022$, $\eta_p^2 = 0.081$], demonstrating participants in the CSTIM group overall had lower vigor, happiness and calmness compared to those in any other group. Finally, an interaction between time and condition was observed for vigor [$F_{(3,62)} = 3.332$, $p = 0.025$, $\eta_p^2 = 0.139$], such that an effect of time was observed for only those in the ASTIM group. Specifically, baseline vigor was significantly higher than post test vigor for the ASTIM group only. See Appendix 1 for a statistical summary of BRUMS data.

Discussion

This study set out to examine the effect of anodal and cathodal tDCS over the DLPFC on executive functioning and working memory abilities, as evaluated using the color-word Stroop and N-Back letter tasks respectively. In line with our first hypothesis, we found performance on both the Stroop and N-Back tasks to significantly improve between baseline and post-tests, confirming the existence of a practice effect for both cognitive tasks. We then evaluated whether anodal and/or cathodal stimulation modulated post test performance on either task compared to sham and control groups. We found that for the Stroop task, both anodal and cathodal stimulation significantly improved accuracy at post test compared to sham and control conditions only for male participants, with no significant difference observed for response time. On the N-Back task, improvements were observed for 2-Back sensitivity in all groups except those in the A-STIM group, where any practice effect on the 2-Back level of the N-Back task appeared blunted. We discuss the relevance of these findings considering the existing work to date investigating the effect of neurostimulation on cognitive abilities.

Overall, research investigating the effect of tDCS on executive functioning and inhibitory control is mixed, particularly among those studies utilizing the Stroop task as a cognitive tool. For example, while Loftus et al. (2015) suggest anodal tDCS augments performance through an observed reduction in response times, they observe an appreciable increase in error rates following tDCS, suggesting a strategy change rather than a cognitive

TABLE 2 Statistical results from 2-way ANCOVAs on all metrics.

Test	Metric	Stimulus type	Effect	df1	df2	*F*-value	*p*-value	Effect size
Stroop	Accuracy (% Correct)	All	Sex	1	69	0.006	0.941	0
			Condition	3	69	1.102	0.355	0.051
			Sex*Condition	3	69	1.602	0.198	0.073
		Control	Sex	1	69	0.178	0.674	0.003
			Condition	3	69	0.869	0.462	0.041
			Sex*Condition	3	69	0.282	0.838	0.014
		Congruent	Sex	1	69	0.514	0.476	0.008
			Condition	**3**	**69**	**3.783**	**0.015**	**0.157**
			Sex*Condition	**3**	**69**	**3.628**	**0.018**	**0.151**
		Incongruent	Sex	1	69	0.19	0.665	0.003
			Condition	3	69	0.512	0.676	0.025
			Sex*Condition	3	69	0.227	0.877	0.011
	Response Time (ms)	All	Sex	1	69	0.851	0.36	0.014
			Condition	3	69	1.858	0.146	0.084
			Sex*Condition	3	69	1.265	0.294	0.059
		Control	Sex	1	69	0.108	0.744	0.002
			Condition	3	69	1.458	0.235	0.067
			Sex*Condition	3	69	1.159	0.333	0.054
		Congruent	Sex	1	69	0.232	0.632	0.004
			Condition	3	69	1.864	0.145	0.084
			Sex*Condition	3	69	0.218	0.884	0.011
		Incongruent	Sex	1	69	2.21	0.142	0.035
			Condition	3	69	1.082	0.364	0.051
			Sex*Condition	3	69	1.91	0.137	0.086
N-Back	D-Prime (d')	1-Back	Sex	1	69	0.315	0.577	0.005
			Condition	3	69	0.334	0.801	0.016
			Sex*Condition	3	69	0.461	0.71	0.022
		2-Back	Sex	1	69	1.685	0.199	0.027
			Condition	3	69	1.355	0.265	0.062
			Sex*Condition	3	69	0.112	0.953	0.005

Bold values denote statistical significance $p < 0.05$.

performance advantage. Alternatively, in a study by Frings et al. (2018), they report an increase in error rate following cathodal stimulation with no effect of anodal stimulation. However, this study failed to compare effects to a control condition and their electrode montages were different to the bihemispheric setup in this experiment. In previous studies by Fecteau et al. (2007; 2014), they fail to report on the effect of tDCS on overall response times, rendering the effect of tDCS inconclusive. Finally, a recent study by Baumert et al. (2020) reported improved response times across the various trial types of the Stroop task. However, no baseline performance was recorded and thus, one cannot say for certain that differences between stimulation groups are not resulting from inherent differences that would have existed following a baseline test prior to any intervention.

In our study, we found that when using a bihemispheric electrode montage, both anodal and cathodal stimulation (with reference to the left-DLPFC), response times and error rates (accuracy) were no different between conditions testing simple attention (i.e., control trials) or more cognitively complex inhibitory stimuli (i.e., incongruent trials). However, we did see that for males specifically, both anodal and cathodal stimulation reduced errors specifically on congruent trials compared to both control and sham conditions, with no difference in response time reductions across stimulation conditions. This finding is not explained by differences in caffeine or alcohol consumption, as all participants reported refraining from alcohol at least 24 h prior and caffeine at least 4–6 h prior to testing. Moreover, we argue that this finding is not explained by a placebo effect as 76% of participants in the sham group reported thinking they were in a neurostimulation

group upon performing a manipulation check at the conclusion of the experiment.

Congruent trials are arguably the easiest trial type presented during the Stroop task, as evidenced by the fact that response times and error rates are the lowest compared to control and incongruent trial types. This is believed to result from semantic facilitation (La Heij et al., 1985; Parris et al., 2022). Moreover, it has also been established on multiple occasions that during the performance of many cognitive tasks, males often prioritize speed over accuracy, with females adopting the opposite, more cautious strategy of prioritizing accuracy (Lohman, 1986; Campbell et al., 2018; Toth and Campbell, 2019). Our findings demonstrate that during the post test (second attempt at the Stroop task), accuracy decreases for males on congruent trials as response times improve, suggesting males potentially gain confidence to adopt a strategy that prioritizes response speed on 'easier' trials. In this case, both anodal and cathodal stimulation appear to facilitate the maintenance of accuracy performance while response times improve. The novelty of this result is noteworthy, as the aforementioned studies investigating the effect of neurostimulation on cognitive ability did not consider the effect of sex due to imbalances in participant recruitment (Loftus et al., 2015; 65% female, Frings et al., 2018; 66% female, Baumert et al., 2020; 73% female). As a result, our finding, albeit exploratory, calls into question the potential for sex to moderate the effect of neurostimulation on cognitive functioning and merits further research. Previous work has suggested differences in skull anatomy to affect the delivery of current to the central nervous system (Zamora et al., 2018; Kwan et al., 2019). However, this topic is only more recently attracting research attention as it relates to tDCS (Hunold et al., 2021; Sun et al., 2021).

When considering our N-Back results, we observed firstly that cathodal stimulation over the left dlPFC did not augment performance compared to sham or stimulation conditions. This aligns with previous work suggesting there is little evidence for cathodal stimulation to hinder working memory performance (Zaehle et al., 2011; Mylius et al., 2012; Keshvari et al., 2013). However, we did observe a trend for anodal stimulation to blunt the practice effect evident for all other conditions. This potential effect may need to be explored further or examined with increases in stimulation dosage across multiple stimulation sessions. However, recent work would suggest that repeated tDCS may not enhance the effect (Mashal and Metzuyanim-Gorelick, 2019). Overall, we did not find any significant effect of a single session of tDCS on working memory performance, a finding shared by others (Hoy et al., 2013).

Previous work has suggested that a bihemispheric bipolar montage of tDCS can be more efficacious than unipolar montages for motor tasks (Waters et al., 2017). However, we did not find any evidence of an enhanced effect from our bihemispheric montage over the dlPFC on cognitive ability. This may not be due to the electrode montage, but the stimulus waveform itself. It has been shown previously that transcranial alternating current stimulation (tACS) may be more efficacious for augmenting cognitive performance as the sinusoidal waveform can be better tuned to the underlying neural rhythms evident during cognitive processing as observed using EEG (Kim et al., 2021). Thus, further work investigating the effect of cathodal vs. anodal bihemispheric tACS on cognitive abilities is warranted.

This study set out to comprehensively investigate the effect that anodal and cathodal bipolar bihemispheric tDCS could have on executive function and working memory abilities. Overall, we provide further evidence that tDCS may not be as efficacious for enhancing cognitive functioning as it has been shown to be for motor learning. We also provide preliminary evidence that the effect of neurostimulation on cognitive functioning may be moderated by sex, with males demonstrating a benefit from both anodal and cathodal stimulation when considering performance on simple attention trial types within the Stroop task. In light of this exploratory finding, we propose a new avenue for tDCS research, that is to investigate the potential for sex to moderate the efficacy of neurostimulation on cognitive functioning.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by EHS research Ethics Committee, University of Limerick. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AT: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – original draft. CH: Data curation, Formal analysis, Investigation, Writing – original draft. HG: Data curation, Formal analysis, Investigation, Writing – original draft. NK: Data curation, Formal analysis, Investigation, Writing – original draft. AB: Conceptualization, Methodology, Writing – review & editing. MC: Conceptualization, Formal analysis, Funding acquisition, Methodology, Resources, Supervision, Visualization, Writing – review & editing.

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Conflict of interest

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2023.1275878/full#supplementary-material

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Efficacy and safety of transcranial pulse stimulation in young adolescents with attention-deficit/hyperactivity disorder: a pilot, randomized, double-blind, sham-controlled trial

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Background: This is the first study to evaluate the efficacy and safety of transcranial pulse stimulation (TPS) for the treatment of attention-deficit/hyperactivity disorder (ADHD) among young adolescents in Hong Kong.

Methods: This double-blind, randomized, sham-controlled trial included a TPS group and a sham TPS group, encompassing a total of 30 subjects aged 12–17 years who were diagnosed with ADHD. Baseline measurements SNAP-IV, ADHD RS-IV, CGI and executive functions (Stroop tests, Digit Span) and post-TPS evaluation were collected. Both groups were assessed at baseline, immediately after intervention, and at 1-month and 3-month follow-ups. Repeated-measures ANOVAs were used to analyze data.

Results: The TPS group exhibited a 30% reduction in the mean SNAP-IV score at postintervention that was maintained at 1- and 3-month follow-ups.

Conclusion: TPS is an effective and safe adjunct treatment for the clinical management of ADHD.

Clinical trial registration: ClinicalTrials.Gov, identifier NCT05422274.

KEYWORDS

efficacy, transcranial pulse stimulation, rct, ADHD, neuromodulation, adolescents

Introduction

Local epidemiological data in Hong Kong suggest that attention-deficit/hyperactivity disorder (ADHD) affects approximately 6% of children and that it is twice as common in males than in females (1). The prevalence of ADHD in adults is approximately 2.5% (2). ADHD is characterized by persistent symptoms of inattention and/or hyperactivity/impulsivity (3) that emerge in childhood (4). These symptoms may persist into adulthood, leading to poor life outcomes and affecting employment and interpersonal relationships (5). ADHD may affect all aspects of an individual's life and has a negative impact on family members (6). The neurobiological mechanism of ADHD may be attributed to dopaminergic imbalance in the forebrain and basal ganglia. The prefrontal cortex, anterior cingulate cortex, insula, amygdala and cerebellum are also linked to ADHD pathophysiology (7). Typical ADHD treatments include pharmacotherapy, with stimulant medications (e.g., methylphenidate, amphetamine) and nonstimulant medications (e.g., atomoxetine) targeting dopaminergic and noradrenergic systems in the frontal cortex and the dopaminergic system in the basal ganglia (8). These drugs are effective and safe for the majority of patients; however, 20% of patients do not tolerate these medications or fail to respond (9). Although these medications can significantly improve ADHD symptoms and patient outcomes, long-term drug compliance is necessary to sustain treatment efficacy (10). Medication dosages also need to be individually monitored to minimize adverse effects while maintaining efficacy (8). It remains debatable whether the long-term benefits of taking medications outweigh the risks in individuals with ADHD.

Medication (e.g., methylphenidate) is usually the first line of pharmaceutical treatment for ADHD symptoms among adolescents, however; medication adherence and its long-term efficacy is always questionable, partially attributed to medication non-adherence and drug attitude. This claim was supported by the results reported by a cross-sectional study (11) comprising 181 adolescents aged 12–18 years old. Half of the study population ($n = 93$; 51%) experienced side effects, such as decreased appetite and sleep problems. Most participants ($n = 150$; 83%) had an indifferent attitude which referred to perceived low necessity and low concerns toward their ADHD medication. More than half of the study population ($n = 111$; 61%) reported 'nonadherent' toward their prescribed medications and thus, researchers work ameliorate hard to investigate other non-pharmaceutical options for this clientele.

Although mindfulness-based cognitive therapy (MBCT) has recently been demonstrated to be an effective psychosocial intervention (12), the long-term sustainability of the benefits of these psychosocial interventions on ADHD has yet to be confirmed. In fact, pharmacotherapy is not considered a monotherapy for more than 50% of adult ADHD cases (13, 14), and a combination of cognitive behavioral therapy (CBT) and medication yields broader improvements in executive functioning than CBT alone.

It is evident that exiting NIBS studies have used EEG-neurofeedback, trigeminal nerve stimulation (TNS), rTMS, and tDCS in different age groups but have reported inconsistent results in individuals with ADHD. Almost all NIBS studies focused on the left/right/bilateral DLPFC in individuals with ADHD. Stimulation targeting the right inferior frontal cortex (rIFC) was shown to be ineffective. Since ADHD is increasingly prevalent in Hong Kong, there is a pressing need to evaluate the efficacy of the latest NIBS technology (i.e., transcranial pulse stimulation, TPS) which has not been tested nationwide. Findings emerge will provide new neuroscientific evidence to determine whether TPS is an effective adjunct treatment for ADHD in clinical psychiatry. Neurobiological mechanism of ADHD may be attributed to dopaminergic imbalance in the forebrain and basal ganglia. The prefrontal cortex, anterior cingulate, insula, amygdala and cerebellum are also linked to ADHD pathophysiology. As plastic cortical changes are considered to be the substrate of learning and memory, both in development and aging, an overview of the relevant literature about neuroplasticity and its modulation in physiological and pathological conditions is mandatory also in adults [for example see (15, 16)], nonetheless, the scope of this paper is to focus on the efficacy of TPS on young adolescents aged between 12 and 17 years old, in particular, we focus on participants' behavioral and cognitive changes after TPS interventions using participants' self-reported data. Although we also aimed to investigate the different neural substrates underpinning neuropsychological performance in our participants in terms of their attention performance, executive memory, and intra-individual variability (IIV) in reaction time. Nonetheless, the intercept of neurophysiological substrates of ADHD with TPS will only be discussed in a separate paper using MRI data analysis [Cheung et al. (17), under review].

Neuromodulation and non-invasive brain stimulation (NIBS)

Designing interventions that could directly modulate brain function has received increasing interest with the development of technology capable of delivering narrow and tailored modulation of specific brain circuits. Noninvasive brain stimulation (NIBS), such as repeated transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), is widely applied with the aim of rebalancing neural activity at the circuit level to normalize functions and behavior. Currently, these NIBS techniques are being used diagnostically and therapeutically for different types of neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's Disease) (18), pediatric epilepsy (19), neuropsychiatric disorders (e.g., attention-deficit/hyperactivity disorder, major depressive disorder, substance use disorder) (20) and neurodevelopmental disorders (e.g., autism) (21). A recent systematic review and meta-analysis (22) of neurotherapeutics for ADHD provided evidence that electroencephalography (EEG)-neurofeedback showed small/medium effects compared to nonactive controls in randomized controlled trials. However, trials evaluating rTMS or tDCS have reported mixed outcomes. Findings regarding rTMS-induced improvements in cognition or symptoms in individuals with ADHD have been inconsistent, while tDCS studies targeting the dorsolateral prefrontal cortex (DLPFC) led to small cognitive improvements in individuals with ADHD. The key findings in specific age groups (e.g., children, adolescents, and adults) of people with ADHD are summarized below (see Table 1).

In summary, previous NIBS studies have used EEG-neurofeedback, trigeminal nerve stimulation (TNS), rTMS, and tDCS in different age groups but have reported inconsistent results in individuals with ADHD. Almost all NIBS studies focused on the left/right/bilateral

TABLE 1 Findings of non-invasive brain stimulation (NIBS) studies on ADHD.

Authors	N	Age	Design	Session/ duration	Treatment region	Results
Transcranial direct current stimulation (tDCS)						
Cosmo et al. (19)	60	18–65	Double-blind, sham-controlled RCT	1	Left DLPFC	No significant differences in ADHD symptoms between the tDCS & sham group
Soff et al. (20)	15	12–16	Double-blind RCT	5	Left DLPFC	Significant reduction of Hyperactivity & Inattention ($p < 0.05$) but no effect on impulsivity
Allenby et al. (4)	37	18–65	Double-blind, sham-controlled RCT	3	Left DLPFC	tDCS improved impulsivity symptoms
Leffa et al. (21)	64	18–60	Double-blind, parallel, sham-controlled RCT	20	Anodal-right and cathodal-left prefrontal	Mean inattention score was 18.88 (SD 5.79) in the active tDCS group compared with 23.63 (SD 3.97) in the sham tDCS. Significant treatment by time intervention evaluated by clinician-administered version of the adult ADHD self-report scale (β interaction: −3.18, $p < 0.001$).
Westwood et al. (22)	50	10–18	Double-blind, sham-controlled RCT	15	rIFC	No significant improvement in core ADHD symptoms ($p > 0.05$)
Repetitive transcranial magnetic stimulation (rTMS)						
Paz et al. (23)	22	12–16	Single-blind RCT	20	Bilateral DLPFC	No effect on clinical/cognitive outcomes ($p > 0.05$)
Cao et al. (24)	64	6–13	3-armed RCT rTMS ($n = 20$); ATX ($n = 19$); rTMS+ATX ($n = 21$) *ATX = Atomoxetine	6 weeks	Right DLPFC	rTMS+ATX group improved significantly in inattention & hyperactivity/impulsiveness at posttreatment ($p < 0.05$). All groups showed improvements in clinical/cognitive measures.
Trigeminal nerve stimulation (TNS)						
McGough et al. (25)	62	8–12	Double-blind, sham-controlled RCT	4 weeks	Right frontal lobe and frontal midline	Significant reduction of ADHD-RS score ($p = 0.005$) and CGI score on active TNS group ($p = 0.003$) compared to sham TNS group

DLPFC, dorsal lateral prefrontal cortex; IFC, inferior frontal gyrus; RCT, randomized controlled trial.

DLPFC in individuals with ADHD. Stimulation targeting the right inferior frontal cortex (rIFC) was shown to be ineffective (23). Since ADHD is increasingly prevalent in Hong Kong, there is a pressing need to evaluate the efficacy of the latest NIBS technology **(i.e., transcranial pulse stimulation, TPS).** Such research would not only generate new neuroscientific evidence but also reveal whether TPS is an effective adjunct treatment for ADHD. If so, TPS treatment could reduce the global disease burden and psychiatric morbidities (e.g., mood disorders/anxiety disorders, eating disorders, and substance-related disorders) (24, 25) in Hong Kong.

Mechanisms of TPS

TPS uses repeated single ultrashort pulses in the ultrasound frequency range to stimulate the brain. With a neuronavigation device, TPS can target specific and precise areas of the human brain (27). TPS differs from tDCS and rTMS because it does not involve direct or induced electric current. Using electric currents to stimulate the brain may be limited by conductivity (28) and failure to reach deep brain regions (29). In contrast, TPS uses low-intensity focused ultrasound, which provides good spatial precision and resolution to noninvasively modulate subcortical areas, addressing the problem of skull attenuation (30). By using lower ultrasound frequencies, TPS can stimulate deep cerebral regions, reaching as far as 8 cm into the brain. In other words, TPS can improve skull penetration in the human brain and improve treatment outcomes (27). Our theoretical basis is based on the biological mechanism of TPS. Mechanotransduction is the basic mechanism of transcranial pulse stimulation. Mechanotransduction is a biological pathway through which the cells convert the mechanical TPS stimulus into biochemical responses, thereby triggering some fundamental cell functions, such as migration, proliferation, differentiation and apoptosis (31). TPS can promote new blood vessel formation (angiogenesis) and nerve regeneration, stimulate vascular growth factors (32, 33) and brain-derived neurotrophic factor (34) and improve cerebral blood flow. TPS can stimulate deep cerebral regions (i.e., 8 cm) into the brain. The ultrashort ultrasound pulse could enhance cell proliferation and differentiation in cultured neural stem cells, which plays an important role in brain function repair in central nervous system diseases (35). TPS may affect neurons and induce neuroplastic effects, which increase cell permeability (35) stimulate mechanosensitive ion channels and release nitric oxide that causes vasodilation, increased metabolic activity and angiogenesis (36). TPS may play an important role in the restoration of brain function in individuals with CNS diseases (35).

Previous research on transcranial pulse stimulation (TPS)

Application of ultrasound to the brain is a revolutionary therapeutic approach for patients with neuropsychiatric symptoms (37, 38). Since transcranial pulse stimulation (TPS) is a relatively new noninvasive brain stimulation (NIBS) technology, only four studies thus far have been conducted in clinical populations. The first study included 35 Austrian older adults with Alzheimer's disease (AD) who were treated with three TPS sessions per week (6,000 pulses each; global brain stimulation) for 2–4 weeks. Participants showed significant improvement in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery scores immediately after the intervention and at 1 month and 3 months after the intervention. The functional magnetic resonance imaging (fMRI) results also showed significantly increased connectivity within the memory network (27). Participants' depressive symptoms were also significantly improved, as measured by the Geriatric Depression Scale (GDS) ($p = 0.005$) and Beck Depression Inventory (BDI) ($p < 0.0001$) at the 1-month and 3-month follow-ups compared with the baseline scores (27). The second TPS study was an open-label single-blind pilot RCT using waitlist control (WC) (39). This study evaluated the efficacy of TPS in people with MDD. A total of 30 subjects (aged 18–51 years) received 6 TPS sessions (400 TPS pulse/session) administered over 2 weeks on alternate days (total TPS pulse: 2,400; frequency: 2.5–3.0 Hz). Significant improvements in depression severity were observed in the TPS group compared with the WC group ($p = 0.02$), and the effect size was very large (Cohen's $d = -0.9$) (39). However, these two studies were uncontrolled studies or open-label RCTs without a sham control group. Placebo effects must be considered when interpreting the results. The third study was a double-blind, randomized, sham-controlled trial evaluating the efficacy of TPS for autism spectrum disorder in 32 young adolescents (27 males) aged between 12 and 17 years in Hong Kong (40, 41). This trial used the same stimulation protocol (energy level: 0.2–0.25 mJ/mm2, pulse frequency: 2.5–4.0 Hz, 800 pulses/session) over 2 weeks on alternate days, but the ASD trial targeted the rTPJ. TPS over the right temporoparietal junction (rTPJ) was effective in reducing the core symptoms of ASD, as evidenced by a 24% reduction in the primary outcome, the Childhood Autism Rating Scale (CARS) score, in the TPS group. Additionally, there was a 53.7% reduction in the CGI total score in the TPS group at the 3-month follow-up compared with baseline values.

To date, there have been no further attempts to apply TPS to treat other neurodevelopmental disorders in children or young adolescents in Hong Kong or China. The impetus of our research was to fill this research gap, providing findings that could be crucial for ADHD symptom management.

Objectives and hypotheses

The aims of this study were as follows: (i) to evaluate the efficacy and safety of TPS in young adolescents (aged 12–17 years) with ADHD in Hong Kong; (ii) to examine the associations of TPS with ADHD core symptom severity, executive function, inattention, hyperactivity, impulsivity, and oppositional defiance; and (iii) to examine brain functional connectivity changes after 2 weeks of TPS treatment by neuroimaging data. Based on our recent TPS study on ASD young adolescents, we hypothesized the expected outcomes as follows:

Primary hypothesis

The TPS group will have a 30% reduction in the Swanson, Nolan, and Pelham Teacher and Parent Rating Scale (SNAP-IV) score (i.e., inattention, hyperactivity/impulsivity and oppositional defiance) after 2 weeks of TPS treatment compared with the sham TPS group, and this reduction will be maintained at the 1-month and 3-month follow-ups. We set up the hypothesis of 30% improvement of ADHD symptoms in the TPS group is based on a similar published double-blinded RCT using TPS on Autism Spectrum Disorder (ASD).

Secondary hypotheses

1 Young adolescents with ADHD in the TPS group or the sham TPS group will have <5% increase in somatic discomfort in the 2-week TPS intervention.
2 The TPS group will have 30% improvement in ADHD symptoms and behavior compared with the sham TPS group after 2 weeks of TPS treatment, and this improvement will be maintained at the 1-month and 3-month follow-ups.
3 The TPS group will have 30% improvement in executive function after 2 weeks of TPS treatment compared with the sham TPS group, and this improvement will be maintained at the 1-month and 3-month follow-ups.
4 The TPS group will have 30% improvements in attention deficit, hyperactivity and impulsivity after 2 weeks of TPS treatment compared with the sham TPS group, and this improvement will be maintained at the 1-month and 3-month follow-ups.
5 The TPS group will have more brain connectivity changes after 2 weeks of TPS compared with the sham TPS group, and this difference will be maintained at the 1-month and 3-month follow-ups.

We set up the hypothesis of 30% improvement of ADHD symptoms in the TPS group was based on a similar published double blinded RCT using TPS on young adolescents (age 12–18) with Autism Spectrum Disorder (41) which led to a 24% reduction in the Childhood Autism Rating Scale (CARS), the primary outcome of this trial (41). We speculated the 5% increase in discomfort for the sham TPS group was based on the following arguments:

1 headache/pain is the most common adverse effect reported in three trials: (1) TPS randomized, sham-controlled trial on young adolescents with Autism Spectrum Disorder (41); (2) TPS randomized controlled trial using waitlist control on patients with Major Depressive Disorder (age 18–65) (39); and (3) the first open-label study that tested the efficacy of TPS on older adults (age 65+) with Alzheimer's Disease (27). These three published trials had a < 4% adverse effect in either the TPS group or the sham group/waitlist control group.
2 There is cumulative evidence suggesting that placebo effect is a neurobiological phenomenon in different methodological approaches (42). In this study, participants in the sham TPS

group may have the belief/desire that they were being administered a verum TPS and such expectation of this treatment may create uncertainty about the sensory information of pain/discomfort, leading to a placebo effect of a perceptual error (43, 44).

How was the protocol determined in this study?

The first TPS study nationwide was conducted on 35 adult patients with Alzheimer's disease and researchers used 6,000 TPS ultrashort ultrasound pulse (energy level: 0.2–0.3 mJmm −2; pulse frequencies of 1–5 Hz pulse per second) on each patient in each session throughout the 2-weeks' interventions (27). Only 4% reported adverse effects during TPS but none required pain analgesics or other treatment.

Prior to this study, we also adopted a similar double-blind, randomized, sham-controlled trial on young adolescents with autism spectrum disorder (aged 12–17 years), but we used 800 TPS pulse (energy level: 0.2–0.3 mJmm −2; pulse frequencies of 2–4 Hz pulse per second) in each session, administered in 6 sessions spanning across 2-week period, as we only targeted on the rTPJ (right temporoparietal junction). Only 1/3 of participants out of 15 in the TPS group reported transient headache on a numerical pain score of 3–5 out of 10 but none of these participants required any pain analgesics after the intervention (41).

In this study, we also targeted on young adolescents aged between 12 to 17 years old with ADHD, but this time we targeted on the left DLPFC as the treatment region, the project team decided to adopt the same protocol as used in our ASD study. Both ASD and ADHD study had sought safety approval with the TPS expert team including the TPS manufacturer, neurologist, and mathematician within the Project team (27).

Methods

Trial design

This study was a two-armed, randomized, double-blind, sham-controlled trial that evaluated the efficacy and safety of 2 weeks of TPS for treating ADHD among young adolescents. The trial design complied with the Consolidated Standards of Reporting Trials (CONSORT) statement (45). Participants were randomly allocated to the TPS group or sham TPS group. All parents of participants were informed about the randomization procedures and that their children had a 50% chance of receiving the TPS or the sham TPS treatment. This study was conducted in accordance with the Declaration of Helsinki (46). Both groups were assessed at baseline (T1), immediately after the 2-week intervention (T2), and at the 1-month and 3-month follow-ups (T3, T4) (47) (Figure 1).

Subjects

Participants were recruited via a mass email invitation attached to a poster with a QR code that was delivered by collaborators in the Hong Kong Association for ADHD, CUHK, and HKU. A poster with a QR code was also posted in communal areas on campus. The recruitment period was 1 June to 30 September 2022.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (i) SNAP-IV score ≥ 2; (ii) confirmed diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5); (iii) Han Chinese ethnicity, aged 12–17 years, with no other mental disorders (e.g., intellectual disability disorder) or organic brain diseases that affect cognitive functions; (iv) no severe systemic diseases including heart, liver, lung, and kidney diseases; (v) IQ >80 according to the Stanford-Binet Intelligence Scales, 5th edition (SB-5); and (vi) written parental consent for TPS treatment and neuroimaging.

The exclusion criteria were as follows: (i) did not take ADHD medications in the past 2–4 weeks; (ii) received TMS/rTMS/tDCS or electroconvulsive therapy in the past 12 months; (iii) use of monoamine oxidase inhibitors in the past 14 days; (iv) a history of epilepsy, brain trauma, brain surgery/brain tumor, brain aneurysm or other concomitant unstable major medical conditions such as haemophilia or other blood clotting disorders or thrombosis; (v) communicative impairment; (vi) metal implants in the brain treatment region/artificial cardiac pacemaker; (vii) use of corticosteroids within the last 6 weeks before the first TPS treatment; or (viii) history of micro-cavernomas.

Sample size

To our knowledge, no prior interventional study has evaluated the efficacy of TPS for ADHD. Based on our previous open-label pilot RCT (39) evaluating the use of TPS in adults with MDD that showed a large effect size ($d = 0.91$), we predicted that we would observe a large effect of TPS in this study. We used G*Power version 3.1.9.4 to calculate the target sample size. With a statistical power of 95%, a significance threshold of 0.05, a medium between-group effect size (d) of 0.91, and 4 measurement time points, we calculated that each group would need to include 15 subjects. Thus, a total sample size of 30 was needed. The attrition rate in our pilot MDD trial was 0%. We expected that the attrition rate in this ADHD trial would be <5%. Subjects who dropped out of the 2-week intervention period were replaced by another enrolled subject in this pilot study.

Screening and self-administered questionnaire

The parents of participants completed an online application (accessed via QR code) that collected information on sociodemographic characteristics (age, sex, educational background, monthly family income, living circumstances, school year, participant's psychiatric history and duration of ADHD diagnosis (in years/months), age at diagnosis, duration of prescribed medication use (in years/months), current drugs and dosages, and family history of psychiatric disorders).

Eligible subjects then completed the screening tool (the Swanson, Nolan, and Pelham Teacher and Parent Rating Scale; SNAP-IV). Those with a mean SNAP-IV score ≥ 2 were included. Subjects' medical

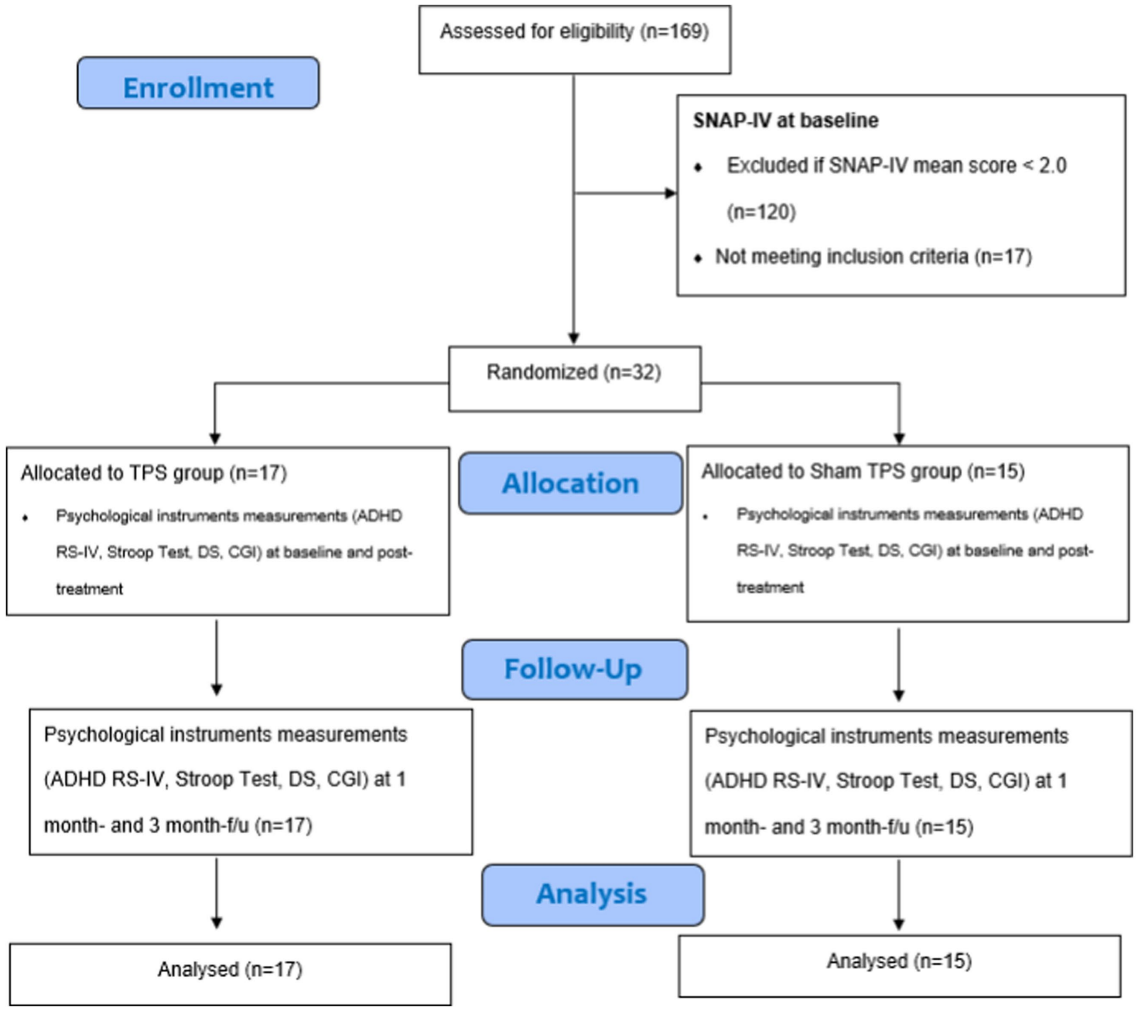

FIGURE 1
CONSORT diagram of procedures. SNAP-IV, Swanson, Nolan, and Pelham Teacher and Parent Rating Scale; ADHD RS-IV, ADHD Rating Scale–IV; DS, Digit Span; CGI, clinical global impression.

history, treatment regimen, and developmental history were obtained by direct enquiry with subjects' parents by online interview prior to neuroimaging and TPS treatment. Both participants and parents were interviewed by the PI and the research personnel. Parents were asked to provide a valid medical certificate of their children's ADHD diagnosis and prescribed formulation sheet during the online interview. Any parents who failed to provide these documents were not invited to participate in this trial.

Randomization, allocation, and masking

All consenting participants were listed in alphabetical order according to their surnames, and each participant was assigned a unique identifier. Participants and their parents were informed that this study involved random allocation to a sham or treatment group. An independent statistician used a computer-generated list of random numbers (www.random.org) to ensure concealment of randomization. Randomization was conducted by an independent statistician off-site using a stochastic minimization programme to balance the sex, age and SNAP-IV scores of the participants. Block randomization with blocks of 10 participants (total: 3 blocks) was used to allocate treatment groups. Participants from each block were randomly assigned to the TPS group or the sham TPS group at a 1:1 ratio. To avoid information flow, participants/parents and research associates were blinded to group allocation to minimize potential contamination of the effects of TPS or subject bias. The experimenter was not involved in data collection or pre- and post-TPS measurements. Outcome measurements were collected by a research associate not involved in group allocation. Participants and their parents were asked to guess their group (TPS vs. sham TPS) in the last TPS session to determine the probability of guessing the group allocation correctly and thereby assess subject blinding (48).

Intervention

TPS intervention was performed at the Integrative Health Clinic at the Hong Kong Polytechnic University (PolyU). A licensed mental health practitioner delivered the intervention. In this trial, we targeted

the left dorsolateral prefrontal cortex (DLPFC). This brain region was selected based on previous tDCS research showing that the left and right DLPFC (49) are primarily the brain treatment regions for ADHD and that stimulation of the left DLPFC, specifically, can improve inattention and hyperactivity (4, 26).

TPS procedures

The TPS system consisted of a mobile single transducer and an infrared camera system for MR-based neuronavigation (NEUROLITH, Storz Medical AG, Tägerwilen, Switzerland). During TPS, single ultrashort (3 μs) ultrasound pulses were generated with typical energy levels of 0.2–0.25 mJ/mm2 and pulse frequencies of 4–5 Hz (pulses per second). During the TPS session, participants sat in a comfortable chair in the treatment venue. Participants wore a BodyTrack® system consisting of a 3D camera, tracking glasses with markers, and a TPS handpiece with markers. This BodyTrack® system ensured that the participant's head matched the T1-weighted images previously obtained at the University Research Facility for Behavioral and Systems Neuroscience (UBSN), PolyU, to allow each TPS pulse to be visualized and documented in real time. Real-time tracking of the handpiece position enabled automatic visualization of the treated brain region. The energy applied is highlighted in green in the figure (Figure 2). The experimenter used the variable stand-offs at the handpiece for depth regulation and manual movement of the handpiece over the skull with real-time visualization on participants' MRI brain images. The whole treatment session was recorded for *post hoc* evaluation of the locations of the individual intracerebral pulses.

TPS intervention dose

In this proposed study, we delivered 800 pulses to the subject's left DLPFC in each session (total: 4,800 pulses). All participants (in both the active and sham TPS groups) received six 30-min TPS sessions over a 2-week period (i.e., 3 sessions/week, on alternate days, total treatment time: 3 h) using energy levels of 0.25 mJ/mm2 and a frequency of 4 Hz. We believe that a two-week TPS intervention is sufficient to test the efficacy of TPS for ADHD (27, 39). Participants were assessed immediately after stimulation (at 2 weeks) and at 1 month and 3 months after the intervention (Figure 1). Also, a posttreatment follow-up at 3 months is sufficient to evaluate the sustainability of TPS for ADHD (27, 39).

For the sham TPS group, participants were given an identical TPS intervention dose, but the silicone oil used in the TPS group was replaced by an air-filled cushion in the handpiece. Participants heard sounds and saw stimuli similar to those of the TPS group.

Fidelity

To ensure the fidelity of the intervention, the project team ascertained whether the interventions were delivered as intended. The experimenter (PI) has a PhD in Social Sciences (HKU) and is a UK & HK licensed mental health professional with more than 10 years of clinical experience in mental health and neuroscience. The research associates provided WhatsApp message reminders (e.g., of the TPS intervention schedule, fMRI scan appointments, follow-up appointments) to parents to monitor subjects' progress, adverse effects and treatment adherence throughout the trial period.

Safety, adverse effects and risk indicators of TPS

TPS uses very low energy for brain stimulation; thus, TPS intervention should not cause any serious adverse effects, such as intracranial bleeding, oedema or other intracranial pathology, as confirmed in previous studies (27, 39). Although this TPS system received clinical certification (CE), indicating that it is a safe intervention, we prepared a checklist of all the potential adverse effects associated with TPS, and monitored subject tolerability and adverse events in each session throughout the trial period. In the pilot RCT on MDD (39), a few subjects reported transient headache (<2 h) (4%), but none required analgesics. Nonetheless, all subjects were covered by master trial insurance in this study.

Ethical and data security considerations

Participant data from both groups were stored in two separate datasets with an identifier linking these data. Both sets of data were encrypted using TrueCrypt (http://www.truecrypt.org). The data from the baseline and the 12-week follow-up were linked according to personal data. All precautions in data protection were taken, as suggested by TrueCrypt. To prevent leakage of personal data, only the PI had access to the personal dataset. Written consent was obtained from all participants and both of their parents prior to the study. An information sheet containing the purpose of this trial and potential risks and benefits of its procedures regarding MRI scans performed at UBSN/PolyU and TPS was provided to all parents. The parents of participants were informed that their children's data would be anonymized and that withdrawal or noncompliance would not result in any consequences.

Measures

Demographic data

Basic demographic data, including age, sex, body mass index, years of education, birth history, number of siblings, monthly household income, and first-degree family members' history of ADHD (yes/no), were collected upon study entry. Details of the subjects' psychiatric history, including the age at diagnosis and any developmental delays or serious injury of any body parts or serious physical illness (es), were also recorded at the baseline assessment.

Attention deficit, hyperactivity impulse, and oppositional defiance

The Swanson, Nolan, and Pelham Teacher and Parent Rating Scale (SNAP-IV) was used to measure inattention, hyperactivity/impulsivity and oppositional defiance. The SNAP-IV consists of 26 items summarized into three factors: inattention, hyperactivity/impulsivity, and oppositional defiance. Based on their general impressions of their children, parents rate the severity of symptoms on a Likert scale (from 0 to 3). A mean score ≤ 1 indicates "normal" or "remission"; a mean

FIGURE 2
Subject's MRI T1-weighted images. The stimulated treatment region (left dorsolateral prefrontal cortex) after transcranial pulse stimulation session.

score of 1 indicates inattention and hyperactivity/impulsivity; and a mean score ≥ 2 indicates "abnormal." The SNAP-IV is a reliable and valid scale used in RCT (50) and has good psychometric properties in the Chinese population (51).

Clinical global impression (CGI)

The Clinical Global Impression Severity (CGI-S) and Improvement (CGI-I) scales are generally used to assess illness severity and global improvement. The CGI-S is a 7-point clinician-rated scale completed based upon observed and reported symptoms, behavior, and function in the past 7 days. The CGI-I is a 7-point scale used to assess whether the patient's ADHD has improved or worsened compared to the baseline. These two scales are complementary (52) and have been used in a double-blinded placebo-controlled RCT (53).

Executive function

The Stroop test is a neuropsychological test commonly used to assess the inhibitory control component of executive function by testing the subject's ability to inhibit cognitive interference that occurs when the processing of the target stimulus feature is impeded by the simultaneous processing of a second stimulus attribute (54).

ADHD symptoms and behavior

The ADHD Rating Scale–IV (ADHD RS-IV) (55, 56) is a widely used ADHD scale comprising 18 items. This scale is completed by the participant's parent, who rates the frequency of each symptom. Each item is scored on a 4-point Likert scale (0: never or rarely, 1: sometimes, 2: often, and 3: very often). The 9 odd items evaluate attention deficits, composing the Inattention (IA) subscale; the 9 even items evaluate hyperactivity/impulsivity, composing the Hyperactivity Impulsivity (HI) subscale; the total score is the sum of all the scores on the 18 items. The ADHD-RS-IV is a reliable and valid scale for use in the Chinese population (57).

Statistical analyses

All statistical analyses were performed using the statistical software R for Windows (R version 4.1.0). Means and standard deviations (SD) of the continuous variables are presented, while numbers and percentages are shown for the categorical variables. A p value <0.05 was considered statistically significant. Sociodemographic differences between the TPS group and the sham TPS group were identified using the chi-square test and Student's t test. If there were significant group differences in sociodemographic factors, these variables were considered confounding variables and included as covariates in the analyses. Normality of the primary outcome (SNAP-IV scores) was determined by the Shapiro–Wilk test for each combination of factor levels (group and time). A Student's t test was used to test the difference in these factors between baseline and the

other time points. A linear mixed model was used to examine the group (between-subject factor; TPS and sham TPS), time (within-subject factor), and group × time interaction effects on SNAP-IV scores. *Post hoc* comparisons between groups and time points were conducted using Student's t tests with Bonferroni correction. The normality of the secondary outcome was determined by the Shapiro–Wilk test at each time point. For normally distributed outcomes, a linear mixed model was used to determine whether the outcome scores significantly differed between pre- and posttest. For outcome scores that grossly deviated from normality, a nonparametric Friedman test was used to determine the mean difference. The effect size of each outcome (Cohen's *d*) was calculated, with $d = 0.2$, 0.5, and 0.8 corresponding to small, medium, and large effect sizes (58). Missing data were managed by multiple imputation (59).

Results

Sociodemographic differences between the TPS and sham TPS groups

There were no statistically significant differences in sociodemographic characteristics between the TPS group and the sham TPS group (all $p > 0.05$). The mean age of the participants was 13.1 years (SD = 1.44). There were more male participants (78%) than female participants. All participants were currently taking medication (methylphenidate HCL), with more than half of the participants (56%) reporting good drug compliance and 62% reporting adverse effects after taking medication. Of these participants, 43% (n = 5) had a family history of psychiatric disorders (ADHD, dyslexia, MDD, anxiety disorder, Asperger's disease), 34% (n = 11) had siblings with psychiatric disorders/problems (i.e., autism spectrum disorder, ADHD, dyslexia, and language delay), 81% had married parents, 94% had obtained secondary education or above, and 59% had a parent that was a homemaker. Other participants (41%) had parents working in semiskilled occupational sectors (see Supplementary Table S1).

Adverse effects, safety issues, and treatment compliance

Overall, three subjects in the TPS group reported transient mild headache during TPS administration, with a mean pain score of 4 out of 10 (range: 0 = no pain to 10 = very severe pain). The pain duration was less than 3 min. No analgesics were required by any subjects, and no parents reported any adverse effects after TPS to the research team. No subjects/parents reported adverse effects in the sham TPS group. In this study, the attrition rate was 0% at all time points. The treatment compliance rate was 100%, which is considered highly encouraging.

Effects of TPS

None of the primary and secondary outcome scores were normally distributed, as shown in Table 2.

Table 3 shows the group, time, and group × time interaction effects on the primary (SNAP-IV) and secondary outcomes (scores on the ADHD-RS-IV, Stroop test, digit span test (forwards and backwards) and the CGI-S, CGI-I, and CGI total) in the TPS group and the sham TPS group. There were significant interaction effects on scores on the SNAP-IV, ADHD-RS-IV, DS forward (length), CGI-S, CGI-I, and CGI total as well as on reaction times on the Stroop test in the word reading (test 1), colour naming (test 2), and named colour-word (test 3) conditions (all $p < 0.05$). There was no group difference in primary or secondary outcome scores at baseline ($p > 0.05$).

Table 4 shows the results of *post hoc* comparisons between groups at each time point to further elucidate the interaction effects on SNAP-IV (see also Figure 3), ADHD-RS-IV (see also Figure 4), CGI-I, and CGI total scores (see also Figure 5). The TPS group had significantly lower mean SNAP-IV scores at posttest (T2), with a large effect size ($d = 0.75$) ($d = 2.45$). Additionally, the TPS group also had significantly lower SNAP-IV scores at the 1-month and 3-month follow-ups (all $p < 0.001$) than the sham TPS group. The effect of group on the primary outcome (SNAP-IV scores) was medium to large (Cohen's *d* values at posttest, 1-month follow-up, and 3-month follow-up: 2.32, 2.45, and 2.40, respectively). Regarding secondary outcomes, the effect on ADHD-RS-IV ($d = 1.04$), CGI-I ($d = 1.04$–5.63), and CGI total scores was large ($d = 1.13$–2.69).

Blinding

In this study, parents were asked to guess the group in which their children were placed to determine the success of the blinding procedures, as some subjects had some difficulty in understanding the concept of blinding. In the TPS group, 76.5% ($n = 13$ out of 17) guessed correctly, while in the sham TPS group, 46.7% ($n = 7$ out of 15) guessed correctly, indicating that our blinding process was successful.

Since some parents in the sham TPS group believed that their children had received the TPS, we analyzed the blinding success between the two groups using the $x2$ test (3.20); the result was not significant ($p = 0.08$), indicating that parents' belief that their child had received active stimulation was not dependent on actual group allocation, confirming that the effect of TPS was solely due to the actual stimulation rather than a placebo effect.

Discussion

This study is the first RCT to evaluate the efficacy and safety of TPS for ADHD in Chinese young adolescents. Notably, we found that TPS improved ADHD core symptoms, and the effects were sustained at the 1- and 3-month follow-ups. Our results are supported by a recent double-blind, sham-controlled trial administering transcranial random noise stimulation (tRNS) (60) to 23 children aged 6 to 12 years. Subjects received 10 sessions of tRNS over the inferior frontal gyrus (rIFG) and left dorsolateral prefrontal cortex (lDLPFC) plus cognitive training (CT) over 2 weeks. The authors reported that tRNS was effective in reducing ADHD symptoms (evaluated by ADHD-RS-IV scores), as revealed by a comparison of the tRNS+CT group and the sham tRNS+CT group. The posttreatment effect size was $d = 2.4$ and dropped to 1.7 at the 3-week follow-up.

Our findings may substantially impact patients and their caregivers as well as the larger community. These results can inform health policymakers regarding the ability to use TPS as an adjunct treatment in the clinical setting in psychiatry, given that both conventional treatments (medication and psychotherapy) involve long-term input to sustain the therapeutic effects in individuals with

TABLE 2 Normality of the primary and secondary outcome scores tested by the Shapiro–Wilk test for each time point.

	Overall	Baseline	Posttest	1-month f/u	3-month f/u
	p	*p*	*p*	*p*	*p*
SNAP-IV total	0.009**	0.75	0.06	0.51	0.41
SNAP-IV mean score	0.02*	<0.001***	0.33	0.22	0.35
ADHD RS-IV	0.02*	0.38	0.39	0.89	0.55
Strooptest1 (reaction time)	<0.001***	<0.001***	0.10	<0.001***	0.03*
Strooptest2 (reaction time)	<0.001***	0.05*	0.22	0.03*	<0.001***
Strooptest3 (reaction time)	<0.001***	<0.001***	0.006**	<0.001***	0.02*
DS-Forward	<0.001***	0.004**	<0.001***	0.002**	<0.001***
DS-Backward	<0.001***	0.04*	0.12	0.11	0.27
DS-Forward (length)	<0.001***	<0.001***	<0.001***	0.89	0.24
DS-Backward (length)	<0.001***	<0.001***	0.006**	0.008**	0.56
CGI-Severity	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***
CGI-Improvement	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***
CGI-Efficacy	<0.001***	<0.001***	<0.001***	<0.001***	<0.001***
CGI-Total	<0.001***	<0.001***	<0.001***	0.05	<0.001***

SNAP-IV, Swanson, Nolan, and Pelham Teacher and Parent Rating Scale; ADHD RS-IV, ADHD Rating Scale–IV; DS, digit span; CGI, clinical global impression.
***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

TABLE 3 The group, time, and group x time interaction effects of the outcomes between the TPS group and the sham TPS group.

	Group	Time	Group x time
	p	*p*	*p*
SNAP-IV mean score	0.94	<0.001***	<0.001***
ADHD RS-IV	0.26	<0.001***	<0.001***
Strooptest1 (reaction time)	0.22	0.61	0.03*
Strooptest2 (reaction time)	0.11	0.04*	0.02*
Strooptest3 (reaction time)	0.04*	0.18	<0.001***
DS-Forward	0.60	0.89	0.71
DS-Backward	0.003**	0.75	0.07
DS-Forward (length)	0.71	0.29	<0.001***
DS-Backward (length)	0.03*	0.49	0.06
CGI-Severity	0.82	0.10	0.002**
CGI-Improvement	0.63	<0.001***	<0.001***
CGI-Efficacy	0.41	0.16	0.69
CGI-Total	0.33	<0.001***	<0.001***

Adjusted for age, gender, and drug compliance. SNAP-IV, Swanson, Nolan, and Pelham Teacher and Parent Rating Scale; ADHD RS-IV, ADHD Rating Scale–IV; DS, digit span; CGI, clinical global impression.
***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

ADHD. These treatment methods inevitably increase health costs, the caregiving burden and the global disease burden. We showed that TPS is effective in the treatment of ADHD patients, providing hope for patients' families and reducing their psychological burden to a large extent because ADHD is curable and treatable by TPS. This represents a breakthrough in neuroscience research for adolescents with special education needs (SEN) in Hong Kong.

Primary outcome measure

Snap-IV

In the TPS group, mean SNAP-IV scores (a measure of ADHD symptom severity) exhibited a 44% reduction by the posttreatment time point; in the sham TPS group, a 20% reduction in these scores was observed. There was a further reduction in the scores of the TPS group at the 1-month (52%) and 3-month (48%) follow-ups, while the sham TPS group exhibited a 16% reduction at both of these time points. The changes in SNAP-IV scores significantly differed between the TPS and sham TPS groups at posttreatment and at the 1-month and 3-month follow-ups (all *p*s < 0.001). In addition, the effect size was large, with Cohen's *d* values ranging from 2.32 (posttreatment) to 2.45 (1-month follow-up) and 2.40 (3-month follow-up) (Table 4).

Secondary outcome measures

ADHD-RS-IV

A 30% reduction in ADHD-RS-IV scores is considered to reflect a clinically acceptable ADHD treatment response (61, 62). We found that 41.1% of participants in the TPS group achieved a clinically effective treatment response at posttreatment compared to 19.1% of participants in the sham TPS group. In addition, 39.7 and 35% of participants in the TPS group achieved an effective treatment response at the 1-month and 3-month follow-ups, respectively, while 13.9 and 17.4% of participants in the sham TPS group achieved such a response (Table 4). The changes in ADHD-RS-IV scores were marginally significant at posttreatment ($p = 0.07$), significant at the 1-month follow-up ($p = 0.01$), and nonsignificant at the 3-month follow-up ($p = 0.14$).

The study showed an initial and 1-month post-treatment improvement in fundamental ADHD symptoms, but this was not maintained at the 3-month follow-up. The likely reason for this is that the initial TPS protocol was only an estimate, as no previous TPS studies had targeted the ADHD population. Factors such as the total number of stimulation pulses and the pulse repetition rate could influence the effectiveness of the TPS treatment for ADHD symptoms. The findings suggested that these TPS parameters are safe for use in young adolescents, with effects gradually appearing after stimulation. However, the energy supplied may not be enough to modify all ADHD symptoms. This underscores the need for larger-scale research and the development of a standard protocol to maximize therapeutic benefits for the ADHD population.

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TABLE 4 *Post-hoc* comparisons between the TPS group and the sham TPS group at each time point.

	Time	TPS Mean (SD)	Sham TPS Mean (SD)	*p*
SNAP-IV (mean)	Baseline	2.5 (0.20)	2.5 (0.24)	0.83
	Posttest	1.1 (0.34)	2.0 (0.43)	0.00***
	1-month f/u	1.3 (0.30)	2.1 (0.35)	0.00***
	3-month f/u	1.2 (0.39)	2.1 (0.36)	0.00***
ADHD RS-IV	Baseline	41.1 (7.27)	40.9 (8.13)	1.00
	Posttest	24.2 (12.28)	33.1 (12.41)	0.07
	1-month f/u	24.8 (10.85)	35.2 (9.08)	0.01*
	3-month f/u	26.8 (13.21)	33.8 (10.34)	0.14
Strooptest1 (reaction time)	Baseline	18.5 (9.58)	14.6 (3.76)	0.05
	Posttest	14.4 (3.62)	15.2 (4.60)	0.79
	1-month f/u	14.1 (5.60)	13.0 (3.34)	0.77
	3-month f/u	12.7 (3.72)	13.2 (3.77)	0.74
Strooptest2 (reaction time)	Baseline	19.2 (5.05)	17.0 (4.99)	0.15
	Posttest	17.1 (4.32)	14.8 (4.31)	0.12
	1-month f/u	15.6 (4.01)	14.0 (4.81)	0.13
	3-month f/u	18.2 (11.13)	14.0 (4.88)	0.18
Strooptest3 (reaction time)	Baseline	29.5 (10.32)	28.0 (15.48)	0.35
	Posttest	26.7 (11.82)	22.0 (8.41)	0.26
	1-month f/u	24.5 (12.46)	18.2 (5.41)	0.11
	3-month f/u	20.0 (7.67)	17.8 (7.10)	0.33
DS-Forward	Baseline	12.3 (1.21)	12.2 (1.70)	0.94
	Posttest	12.2 (1.92)	12.7 (1.23)	0.75
	1-month f/u	12.6 (1.42)	12.5 (1.25)	0.76
	3-month f/u	12.5 (2.04)	12.7 (1.16)	0.81
DS-Backward	Baseline	6.4 (2.96)	7.1 (3.79)	0.76
	Posttest	7.8 (3.03)	7.6 (3.78)	0.73
	1-month f/u	7.4 (2.60)	8.7 (3.50)	0.25
	3-month f/u	8.9 (2.83)	8.5 (3.50)	0.84
DS-Forward (length)	Baseline	5467.1 (558.39)	5332.0 (1367.06)	0.33
	Posttest	4867.1 (711.79)	5008.0 (1531.36)	0.66
	1-month f/u	4482.4 (785.68)	4852.0 (839.35)	0.27
	3-month f/u	4065.9 (865.99)	4244.0 (521.82)	0.50
DS-Backward (length)	Baseline	5371.8 (3245.56)	5420.0 (4798.00)	0.46
	Posttest	6878.8 (4065.36)	6840.0 (4722.72)	0.78
	1-month f/u	6102.4 (2983.96)	7468.0 (3950.89)	0.33
	3-month f/u	8209.4 (3202.09)	7080.0 (3153.69)	0.44
CGI-Severity	Baseline	4.5 (0.62)	4.5 (1.19)	0.60
	Posttest	4.1 (0.90)	4.3 (0.70)	0.72
	1-month f/u	3.7 (0.59)	4.1 (0.74)	0.10
	3-month f/u	4.4 (0.49)	4.4 (0.51)	0.80
CGI-Improvement	Baseline	4.0 (0.00)	4.0 (0.00)	>0.99
	Posttest	2.3 (0.77)	4.0 (0.00)	0.00***
	1-month f/u	1.9 (0.43)	3.9 (0.26)	0.00***
	3-month f/u	1.9 (1.09)	4.0 (0.00)	0.00***
CGI-Efficacy	Baseline	0.1 (0.24)	0.9 (3.36)	0.93
	Posttest	0.0 (0.00)	0.8 (2.83)	0.14
	1-month f/u	0.1 (0.24)	0.1 (0.35)	0.50
	3-month f/u	0.1 (0.33)	0.1 (0.26)	0.65

(Continued)

TABLE 4 (Continued)

	Time	TPS Mean (SD)	Sham TPS Mean (SD)	*p*
CGI-Total	Baseline	8.6 (0.62)	9.3 (3.94)	0.52
	Posttest	6.4 (1.37)	9.1 (3.10)	0.00***
	1-month f/u	5.7 (0.92)	8.2 (0.94)	0.00***
	3-month f/u	6.4 (1.23)	8.5 (0.52)	0.00***

SNAP-IV, Swanson, Nolan, and Pelham Teacher and Parent Rating Scale; ADHD RS-IV, ADHD Rating Scale–IV; DS, digit Span; CGI, clinical global impression.
***$p < 0.001$; *$p < 0.05$.

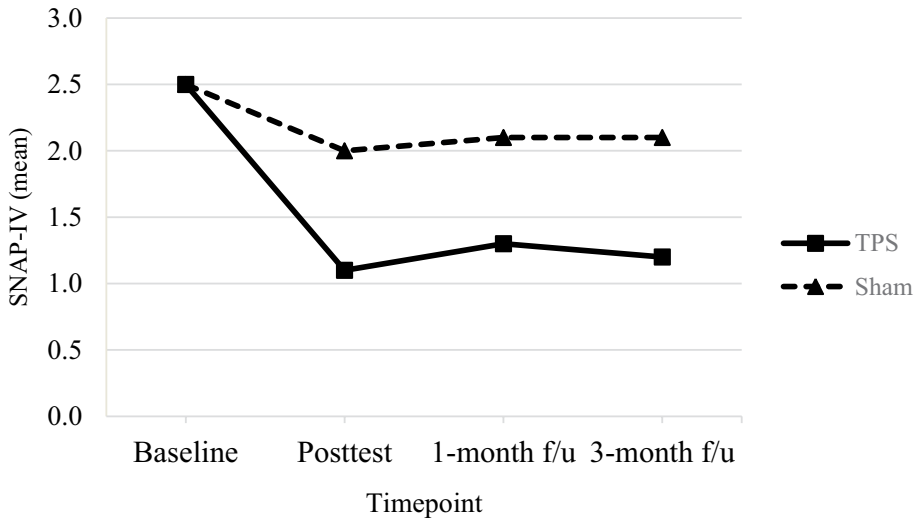

FIGURE 3
Mean scores of SNAP-IV of ADHD participants in TPS and Sham group at different study time points.

Stroop test (1, 2, 3), digit span test (forwards/backwards), digit span (length), CGI-S, CGI-E

There were no statistically significant effects of group on scores on the Stroop test (1, 2, 3), digit span (forwards/backwards), digit span (length), CGI-S, or CGI-E (all *P*s > 0.05).

CGI-I and CGI total scores

Nonetheless, both the mean CGI-I and mean CGI total scores significantly differed between the TPS group and the sham TPS group at posttreatment and at the 1-month and 3-month follow-ups (all *P*s < 0.001). The CGI-I and CGI total scores were provided by the interventionist, and it is encouraging to note that parental ratings of improvement in the TPS group were in line with the professional assessment of the experimenter at all time points.

Our findings regarding the primary outcome (SNAP-IV scores) and one of the secondary outcomes (ADHD-RS-IV scores) of this study are highly encouraging, as both were parent-reported scales that yielded statistically significant differences in the TPS group at all time points. However, there was no effect of treatment on the other secondary measure (that reported by the subjects), particularly in terms of working memory and executive function (EF). This null effect may be explained by the fact that changes in EF may require pharmaceutical input and psychotherapy (for parents/children) over a period of 1 to 3 months (63–66). In other words, monotherapy or TPS alone may have less effect on EF within a short period. The lack of significant difference between the TPS and Sham groups, leading to inconclusive results, could be due to the possible placebo effect impacting the sham participants. This is especially relevant in the context of a randomized-controlled study design (67). In addition, drug adherence may also contribute to the efficacy of TPS in our subjects. Presumably, all subjects took their prescribed medications regularly, but on some occasions, some subjects may have struggled to comply with their current medication regimen due to COVID-19 symptoms (e.g., fever, coughing, physical exhaustion) during the intervention period, despite parental/medical advice. We also speculate that the null effect may also be attributed to the relatively mild or moderate symptom severity and mild executive dysfunction in this sample, as all our subjects were enrolled in mainstream schools in Hong Kong; hence, the effect of treatment on EF may be less prominent in our study. Our results are in line with a pilot study (68) which evaluated the effect of tDCS and tRNS on ADHD symptoms. However, there is no consensus regarding the optimal treatment region in the brain for the treatment/management of ADHD symptoms (49); previous neuroscientific research seems to target the bilateral DLPFC (69), lDLPFC (4), rIFC (70), IFC-parieto-cerebellar networks or prefrontal striatal circuits (71). Future studies should determine the optimal TPS protocol and parameters to yield EF changes in the ADHD population.

In our ADHD protocol (72), we have mentioned that most NIBS studies on ADHD have used EEG-neurofeedback and rTMS/tDCS across different age groups but have yielded inconsistent results in this population. More importantly, most all NIBS studies primarily

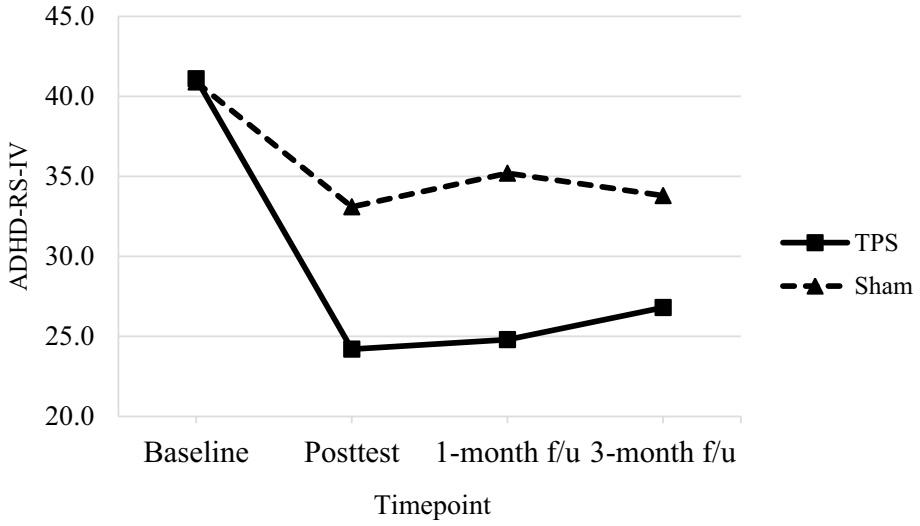

FIGURE 4
Total scores of ADHD-RS-IV of ADHD participants in TPS and Sham group at different study time points.

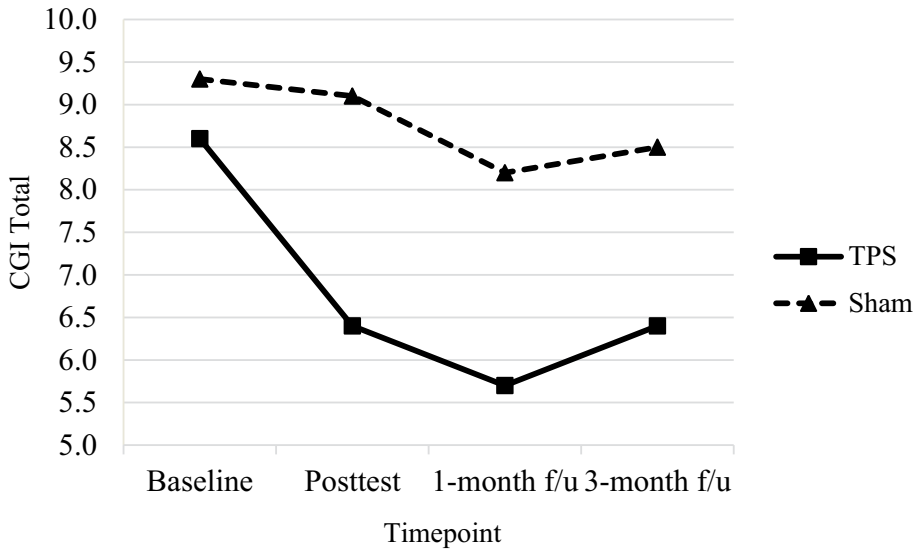

FIGURE 5
CGI total scores of ADHD participants in TPS and Sham group at different study time points.

focused on left/right/bilateral DLPFC (dorsal lateral prefrontal cortex) in ADHD, possibly due to the fact that brain stimulation targeting the right inferior frontal cortex (rIFC) was shown to be ineffective (23). Some studies showed that brain stimulation over the left DLPFC improved the response inhibition, attention, working memory, and cognitive flexibility in ADHD patients (73). Since patients with attention deficit hyperactivity disorder (ADHD) are characterized by both underactivation of the prefrontal cortex and deficits in Working Memory (WM), the modulation of prefrontal activity with TPS in ADHD patients may increase their WM performance as well as improve the activation and connectivity of the WM network (73). Thus, our study findings suggested that TPS caused increased neuronal activation and connectivity, not only in the targeted brain treatment region (i.e., left DLPFC) but also in other remote brain regions which will be covered in another paper which used neuroimaging to evaluate the efficacy of TPS with resting-state MRI (Cheung et al. (17), under review).

At present, there is no standardized TPS protocol on various neurodegenerative diseases and neurodevelopmental disorders. We have reviewed existing TPS randomized controlled trials and other open-label studies with the conclusion (see Supplementary Table S2) that, different non-invasive brain stimulation techniques using RCT sham-controlled design on different ages and clientele seems to demonstrate inconsistent findings. Using our previous double-blind randomized, sham-controlled RCT on ASD as an example, participants in the verum

TPS group had a significant change in the CARs score (primary outcome) immediately after 2-week TPS, and at 1- month and 3-month follow-up compared to the sham TPS. Nonetheless, in this study, participants had significant improvement in the SNAP-IV score, but there was no significant improvement in the ADHD RS-IV in the verum TPS group immediately after the 2-week intervention but became significant again at the post-stimulation at 1-month follow-up and not significant again at 3-month follow-up, when compared to the sham-controlled group. Such intriguing results may be generated from the following speculations:

1 survey/respondent fatigue, which is a well-documented phenomenon (74) when participants are tired of the survey task and the quality of the data may be affected. In this study, ADHD RS-IV was the second psychological instrument which sequentially followed by SNAP-IV. These two sets of surveys have some questions in common and it is plausible that participants' parents were tired when they were asked to answer similar questions in written form which could bias their subjective results toward the participants.
2 Lack of significance between TPS group and the sham TPS group may also attributed to placebo effects in the latter group. Participants in the sham TPS group may have the belief and desire that they were administered the TPS during the treatment process and such belief/desire may bias their subjective data in the self-reported survey (67).

Limitations of the study

Although our study findings demonstrated that TPS is an effective NIBS in the treatment of some ADHD symptoms, there are some limitations that should be addressed. First, this study was a single-site study in Hong Kong with a relatively small sample size. Thus, the findings may not be translatable or generalizable to other country/cultural contexts. Second, we included only subjects enrolled in mainstream schools, and it is not known whether TPS also benefits ADHD patients with severe/very severe symptoms who attend special schools. Third, future studies should include cognitive training in the intervention and use a larger sample size to ascertain whether TPS can be a standalone adjunct treatment. Fourth, despite all participants declared taking prescribed medications throughout the intervention period, only 56% reported good medication adherence and thus, the mean dosage of the medication was not considered as a reliable variable in the statistical analysis.

Conclusion

Our findings provide new understanding and insight into the field of neuroscience. We demonstrated that TPS is an effective, safe, and scientific NIBS that can be used to treat most (but not all) ADHD core symptoms. The long-term effects of TPS require further investigation in multi-national trials. Nevertheless, the incorporation of TPS as a potential means of adjunct treatment option for ADHD should be considered by health policymakers in the near future.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Institutional Review Board, The Hong Kong Polytechnic University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

TC: Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing. BY: Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. BC: Investigation, Validation, Writing – review & editing. JL: Data curation, Formal analysis, Investigation, Project administration, Writing – original draft, Writing – review & editing. KF: Data curation, Formal analysis, Investigation, Project administration, Writing – original draft, Writing – review & editing. HL: Investigation, Writing – review & editing. TL: Formal analysis, Investigation, Methodology, Writing – review & editing. AL: Investigation, Writing – review & editing. LS: Investigation, Writing – review & editing. RB: Conceptualization, Investigation, Validation, Writing – review & editing. CC: Conceptualization, Investigation, Methodology, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1364270/full#supplementary-material

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Theta burst stimulation on the fronto-cerebellar connective network promotes cognitive processing speed in the simple cognitive task

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Background: The fronto-cerebellar functional network has been proposed to subserve cognitive processing speed. This study aims to elucidate how the long-range frontal-to-cerebellar effective connectivity contributes to faster speed.

Methods: In total, 60 healthy participants were randomly allocated to three five-daily sessions of transcranial magnetic stimulation conditions, namely intermittent theta-burst stimulation (iTBS, excitatory), continuous theta-burst stimulation (CTBS, inhibitory), or a sham condition. The sites of the stimulations were the right pre-supplementary motor area (RpSMA), medial cerebellar vermis VI (MCV6), and vertex, respectively. Performances in two reaction time tasks were recorded at different time points.

Results: Post-stimulation speeds revealed marginal decreases in the simple but not complex task. Nevertheless, participants in the excitatory RpSMA and inhibitory MCV6 conditions showed direct and negative path effects on faster speeds compared to the sham condition in the simple reaction time (SRT) task ($\beta = -0.320$, $p = 0.045$ and $\beta = -0.414$, $p = 0.007$, respectively). These path effects were not observed in the SDMT task.

Discussion: RpSMA and MCV6 were involved in promoting the path effects of faster reaction times on simple cognitive task. This study offers further evidence to support their roles within the long-range frontal-to-cerebellar connectivity subserving cognitive processing speed. The enhancement effects, however, are likely limited to simple rather than complex mental operations.

KEYWORDS

fronto-cerebellar, functional connectivity, TMS, cognitive processing speed, reaction time

1 Introduction

Cognitive processing speed (PS-C) refers to the time required to encode an incoming stimulus and connect it with the existing experience in the brain (Kail and Salthouse, 1994). Previous fMRI studies revealed that PS-C is subserved by extensive neural networks. Silva et al. (2018) revealed that performance on a symbol-to-digit task was subserved by an extensive network of middle frontal gyri, superior parietal lobule, precuneus, inferior frontal gyrus, cuneus, and lingual gyrus (Silva et al., 2018). Previous studies quantified processing speed with complex cognitive tests, such as the Symbol Digit Modalities Test (SDMT). A review of these studies indicates their results are inconsistent. For instance, Silva et al. (2019) reported the fronto-parietal and fronto-occipital networks subserved participants' performances in the SDMT (Silva et al., 2019). Savini et al. (2019) revealed that the connectivity between the cerebellum and the default mode network (DMN) was related to the reaction time decline in the SDMT among multiple sclerosis patients (Savini et al., 2019). Manca et al. (2018) conducted a systematic review of multiple sclerosis patients that connectivity of the frontal areas and microstructural integrity of the anterior corpus callosum accounted for processing speed tasks, including SDMT (Manca et al., 2018). The inconsistent results mentioned above could have been confounded by varying contents and task-taking processes of the complex cognitive tasks used in these studies, such as the SDMT.

In a recent study, our research team designed a simple multimodality reaction time task to revisit the PS-C (Wong et al., 2021). This custom-designed task was developed to minimize the potential task-specificity confounds observed in previous studies. The results indicated a fronto-cerebellar connective network, especially long-range effective connectivity in the right medial frontal cortex on the medial cerebellar vermis VI [i.e., Right medial frontal cortex (RMFC) → medial cerebellar vermis VI (MCV6)] subserving PS-C. We further proposed that PS-C is the outcome of an interplay between automaticity and effortful top-down attentional control processes (Wong et al., 2021).

In this study, we aimed to gain a deeper understanding of the roles of the RMFC and MCV6 within the fronto-cerebellar connective network in subserving PS-C. The reason for selecting the RMFC–MCV6 couple for the study is because it was the strongest effective connective predictor of faster reaction times (with the largest β value of −0.330) among the six significant paths (Wong et al., 2021). The RMFC–MCV6 couple is one of the three long-range functional connectivities between the frontal cortex and cerebellum, which involve automaticity and top-down attentional control interplay. The changes in task-based reaction times due to external stimulations applied to the RMFC–MCV6 couple would yield stronger modulation of the fronto-cerebellar connective network than other couples that showed weaker prediction power or belonged to short-range such as the RMFC–LIPS (LIPS refers to left intra-parietal sulcus; β value of 0.301).

Abbreviations: RpSMA, Right pre-supplementary motor area; MCV6, Medial cerebellar Vermis VI; RT, Reaction times; iTBS, Intermittent theta-burst stimulation; CTBS, Continuous theta-burst stimulation; SRT, Simple reaction time; SDMT, Symbol Digit Modalities Test; PS-C, Cognitive processing speed; RMFC, Right medial frontal cortex; RCH6, Right Cerebellum Lobule 6; SEM, Structure equation modeling; RCS, Rate-correct score; MMSE, Mini-Mental State Examination; RMSEA, Root-mean-square error of approximation; CFI, Comparative fit index; TLI, Tucker–Lewis index; SRMR, Standardized root mean square residual.

We employed transcranial magnetic stimulation (TMS) to separately modulate the neural activities of the RMFC and MCV6. Previous studies have demonstrated the effects of TMS on regulating brain activation (Burke et al., 2019) and inducing functional and structural plastic changes (Jung and Lambon Ralph, 2021). The intermittent theta-burst stimulation (iTBS) protocol induced excitatory effects, while the continuous theta-burst stimulation protocol (CTBS) induced inhibitory effects. Other literature employed stimulation to a single neural substrate method to modulate the connectivity of neural networks. For instance, intermittent TBS of the left superior parietal lobule was revealed to enhance cognitive speed and resting-state connectivity of the dorsal attention network (DAN) (Anderkova et al., 2018). Intermittent theta-burst stimulation at the midline cerebellar node of the DAN resulted in improved performances in both sustained and transient attentional control functions, which subserved by the respective connective network (Esterman et al., 2017). High-frequency rTMS of the lateral parietal region was found to effectively improve generic cognitive function via activating the default mode network (DMN) (Wei et al., 2022). The significant single substrate-to-network modulation effects reported in the previous studies lend support to our use of such a method in this study.

The RMFC→MCV6 couple connectivity was a negative relationship (denoted by the →) between the two neural substrates (Wong et al., 2021). That is, the RMFC exerted an inhibitory influence on the MCV6. The negative β value of −0.330 in the regression model suggested that lowering the inhibitory RMFC→MCV6 influence would produce faster PS-C. First, we aimed to increase the inhibitory influence of the RMFC on the MCV6 by applying an excitatory iTBS protocol to the right pre-supplementary motor area (RpSMA). The RpSMA, a subregion of the RMFC (De La Vega et al., 2016), is located in the right prefrontal cortex as part of the salient network (Wang et al., 2020). The RpSMA was found to be related to resource allocation in processing salient information (Weigard et al., 2019) and cognitive control (Wolpe et al., 2022). A previous study of six sessions of excitatory stimulation over the frontal cortex showed increased cognitive performance in patients with Parkinson's disease (Trung et al., 2019). Other studies (Viejo-Sobera et al., 2017; Chung et al., 2019; Dumitru et al., 2020; Wu et al., 2021) reported that the excitatory effects promoted general cognitive functions among healthy subjects and modulated cerebellar-cortical connectivity in patients with progressive supranuclear palsy (Brusa et al., 2014). Second, to produce contrasting effects, an inhibitory CTBS protocol was applied to the MCV6 to suppress its activity. The cerebellar vermis is related to automation, cognitive optimization, and implicit learning (Cheng et al., 2014; Moroso et al., 2017) and modulates neural synchronization in the non-motor frontal cortex (Tremblay et al., 2019). Multiple sessions of inhibitory stimulation over the cerebellar vermis have been revealed to promote synaptic connections (Colnaghi et al., 2017a). In contrast to the facilitative effects mentioned above, other studies reported mixed results of the inhibitory stimulation to the cerebellum.

We hypothesized that iTBS to the RpSMA, which is excitatory in nature, would further increase the negative influence on the MCV6, resulting in higher neural activity to mediate faster reaction times in the participants' post-intervention task performances. In contrast, as the MCV6 receives negative influence from the RMFC (i.e., RMFC→MCV6) to produce faster reaction time, CTBS to the MCV6, which would inhibit its activity, was hypothesized to produce slower

reaction times. We employed a two-task contrast method to quantify the post-stimulation effects. They were the simple reaction time task (SRT), vs the SDMT, a complex reaction time task. The TMS effects were analyzed with repeated measure analysis of covariance (RM-ANCOVA) for the Group × Time on the changes in the task-based reaction times. Structural equation modeling (SEM) was used to model the differences in the TMS modulations of the participants' reaction times on the simple vs complex tasks.

2 Materials and methods

2.1 Subjects

A total of 60 young adults (men: 20; women: 40) were recruited from the university where the study was carried out and its surrounding communities in Fuzhou, China. The participants were randomly assigned to the iTBS, CTBS, or SHAM groups ($n = 20$ each). Their mean age was 23.08 ± 2.31 years, and their years of education ranged from 16.1 to 16.4. All participants had normal or corrected vision without color blindness and normal hearing function of >40 decibels at 500–4,000 Hz. The participants were all right-handed. The exclusion criteria were as follows: participants (1) with a history of known medical, neurological, and mental disorders; (2) with alcohol and other substance abuse habits; (3) with the use of epileptic and hypertension medication; and (4) who are pregnant. Ethics approval was obtained from the Ethics Committee of the Rehabilitation Hospital affiliated with the Fujian University of Traditional Chinese Medicine (No.2019YJS-003-04). All participants provided informed consent before the intake measurement and participation in the experiment.

Sample size calculation was based on the effect size of 0.723 reported in the study by Rastogi et al. (2017), which applied TMS over the lateral cerebellum vs sham. To achieve a power of 0.95 for three groups and four time points at $\alpha = 0.05$, the sample size was 50 participants. With an attrition rate of 15%, the final sample size was 60 participants.

2.2 Study design and experimental setup

This study adopted a randomized, placebo-controlled, and single-blind design. The participants were informed that they would receive one out of three TMS protocols without disclosing their details, such as possible effects or sensations felt. All participants completed the same preparation procedure before the TMS sessions. Both the real and sham TMS were delivered using the same machine. The TMS coils had a comparable outlook and emitted sounds. Group assignment, the delivery of the experimental and control protocols, and the test administration were performed by different research team members. These members did not communicate regarding the study. Depending on the group assignment, the participants completed five consecutive daily sessions of the iTBS, CTBS, or SHAM stimulation protocol (see Figure 1D). The participant sat upright on a comfortable chair with their head in a neutral position. The target brain areas on which the TMS was applied were located by the researcher. After the TMS, the participants completed two cognitive tasks at baseline and at the end of the 1st, 3rd, and 5th TMS sessions.

2.3 Stimulation protocols

The magnetic pulses were delivered by a Magstim Rapid^2 stimulator (Magstim Limited, Whitland, United Kingdom) with a 70 mm diameter figure-of-8 coil. The 80% resting motor threshold (RMT) protocol for pulse intensity was adopted for all participants (Valchev et al., 2016).

The CTBS protocol was applied at the MCV6. The manual navigation method was used to locate the MCV6 because it is situated deep within the cerebellum behind the neck (Montreal Neurological Institute (MNI) coordinates [2.0, −68.6, −20.1]) (Wong et al., 2021). The manual method has been commonly used in other studies involving the cerebellum (e.g., Matsugi et al., 2019; Yao et al., 2022), and the location adopted was 1 cm inferior to the inion (Colnaghi et al., 2017b; Matsugi et al., 2019) (Figure 1A). The parameters for the CTBS were as follows: three-pulse bursts at 50 Hz delivered every 200 ms (5 Hz) (Rastogi et al., 2017) (Figure 1E) at 80% of the resting motor threshold. The total time of stimulation was 40 s (totaling 600 pulses).

The iTBS protocol was applied at the RpSMA. Different from MCV6, locating the RpSMA at the MNI coordinates [6, 20, 44] (Aron et al., 2007) was guided by the BrainSight^2 navigation system (Rogue Research Inc.) (Figure 1B). The stimulation parameters for the iTBS were as follows: three-pulse bursts at 50 Hz every 200 ms in every 2 s train (Figure 1E). The 2 s train of pulses was repeated every 10 s for a total of 190 s (totaling 600 pulses) (Huang et al., 2008).

The SHAM protocol adopted the same parameters as those used for the CTBS but used a sham stimulation coil. The sham coil was placed at the vertex of the participant's scalp (Figure 1C). The parameters for the SHAM condition were as follows: three-pulse bursts at 50 Hz delivered every 200 ms (5 Hz) (Figure 1E). The total stimulation time was 40 s (totaling 600 pulses). The sham coil did not generate any magnetic fields.

2.4 Behavioral test—processing speed tasks

There were four test occasions: baseline, post-TMS1 (1st session), post-TMS3 (3rd session), and post-TMS5 (5th session) (Figure 2). The TMS2 and TMS4 tests were skipped to lower the possible over-practice effects due to the repeated testing among the participants. On each test occasion, participants were asked to complete two cognitive tasks. The two tests were custom-designed to tap into participants' cognitive processing speeds in simple vs complex task-taking processes, i.e., simple reaction time (SRT) and modified SDMT, respectively (Supplementary appendices 1, 2). The tests were constructed with E-Prime 3.0 software (Psychology Software Tools, Inc.) and delivered online. The SRT was used in another study (Deary et al., 2007).

Simple reaction time (SRT): The participant was asked to place a finger on the "0" key; once the "0" appeared on the screen, the participant pressed the key as quickly as possible (Deary et al., 2007). There were 20 trials.

Symbol Digit Modality Test (SDMT): It loads onto attention, processing speed, and working memory (Leavitt, 2021). The electronic version was based on the modified version of SDMT operated on a touch-screen computer (Silva et al., 2018). The

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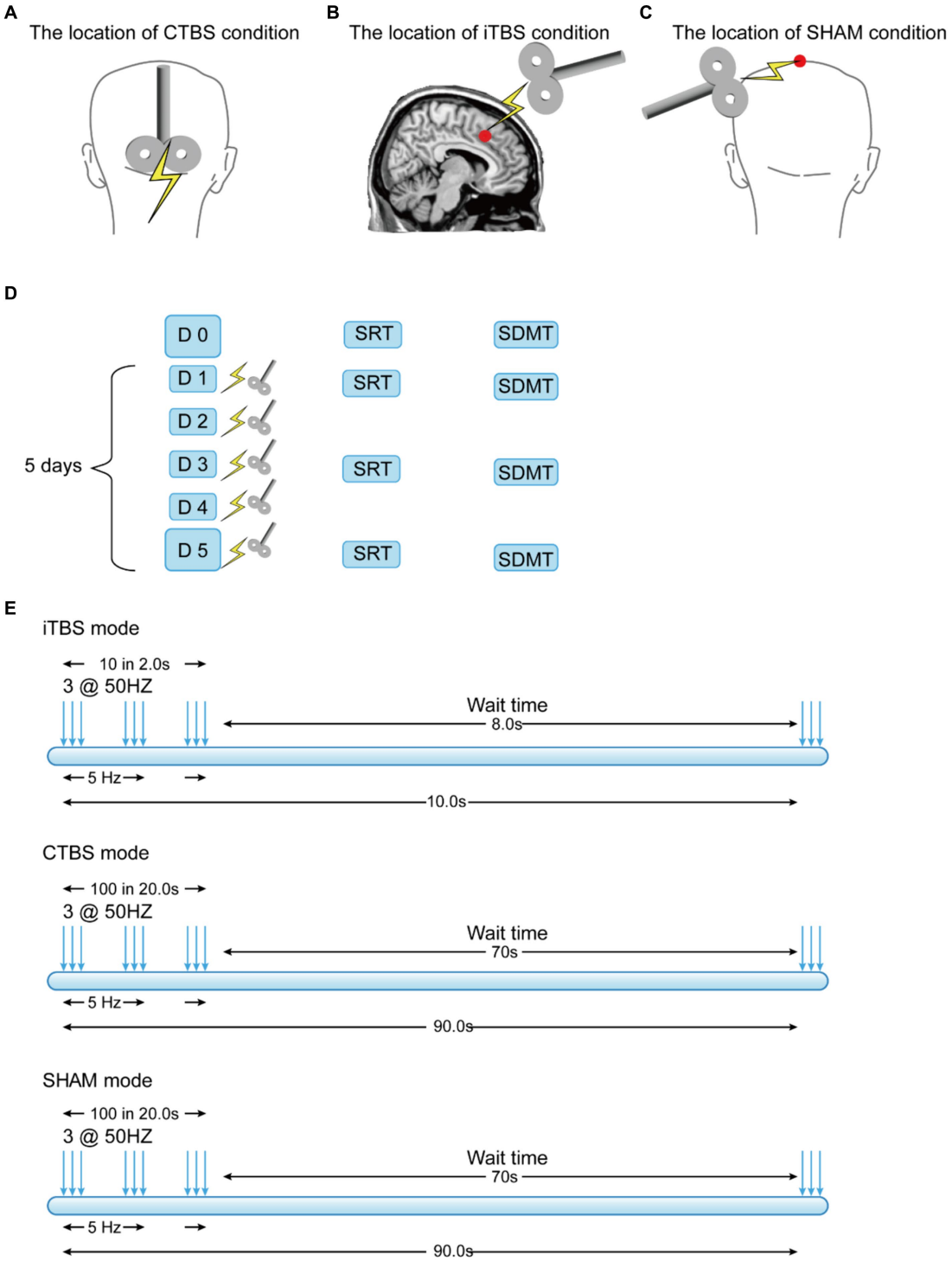

FIGURE 1
Locations over the participants' scalps at which the TMS was applied in three experimental conditions **(A–C)** and the stimulation schedule and protocols **(D,E)**.

modified version was used in two other studies (Gawryluk et al., 2014; Manca et al., 2018). Nine symbol-digit pairs were shown on the upper part of the computer screen as the task keys. Below the symbol-digit pair keys presented a random symbol-digit pair as the stimulus of a trial. The participants were to indicate whether the presented pair would match with one of the nine keys above by pressing "1" (match) or "2" (not match) on the keyboard within 6 s. The symbol-digit pair stimuli were presented in a random order.

Both the reaction times and accuracy of the responses were recorded in each task. The participants were instructed to "complete the task as fast as they could." There was no set time limit for the SRT, but 90 s time limit for the SDMT. Most of the participants completed the SRT in 16 s.

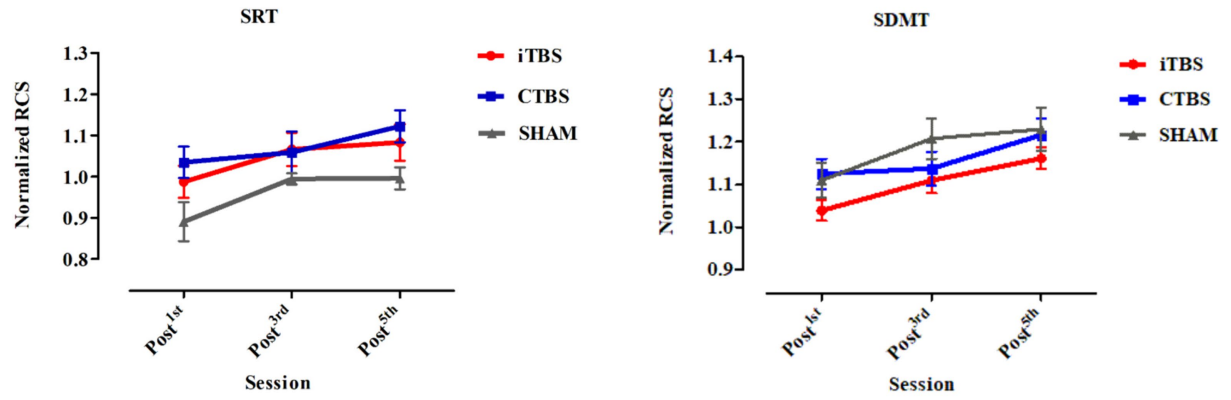

FIGURE 2
Normalized RCS on the SRT and SDMT of participants in the iTBS, CTBS, and SHAM groups on post-TMS1, post-TMS3, and post-TMS5 occasions. RCS, Rate-correct score; SRT, simple reaction time; SDMT, symbol digital modality test. The bars denote the means, and the error bars denote the SEs.

TABLE 1 Demographic characteristics and MMSE scores of participants in the iTBS, CTBS, and SHAM groups.

	iTBS (n = 20)	CTBS (n = 20)	SHAM (n = 20)	χ^2/F	p
Age (Mean/SD)	23.8 (±2.67)	22.5 (±2.19)	23.0 (±1.97)	1.5	0.232
Sex (M/F)	7/13	6/14	7/13	0.15	0.928
Years of education (Mean/SD)	16.4 (±1.19)	16.1 (±1.47)	16.3 (±1.49)	0.34	0.715
MMSE (Mean/SD)	28.5 (±0.76)	28.25 (±1.33)	28.8 (±0.52)	1.73	0.186

MMSE, Mini-Mental State Examination; χ^2/F is Mann–Whitney U-test and one-way ANOVA, respectively.

2.5 Data analyses

All analyses were conducted in accordance with the intent-to-treat (ITT) method (Xi et al., 2018; Andrade, 2022), and no data points were discarded. The participants' demographic characteristics and their SRT and SDMT scores at the baseline were compared. The changes in the reaction times, i.e., the rate-corrected scores, in the SRT and SDMT (see below for the computation) were tested using the 3 × 3 repeated-measures analysis of covariance (RM-ANCOVA) with Group as the between-subject factor (iTBS, CTBS, and SHAM) and Time as the within-subject factor (post-TMS1, 3, and 5). The gender of the participants and their baseline test results were entered as the covariate as women were previously reported to have an advantage over men in processing speed (Siedlecki et al., 2019; Roivainen et al., 2021). Significant Group × Time effects were followed by *post-hoc* pairwise comparison with Bonferroni's adjustment. Statistical significance for the comparisons was set at $p = 0.001$ (0.05/28) (two-tailed) after Bonferroni correction to the number of repeated measures. The software used for all tests was STATA version 17.0.

The rate-correct score (RCS) method (Liesefeld and Janczyk, 2019) was adopted to combine the RTs and accuracy rates for the SRT and SDMT of the participants. The RCS was derived for each participant who performed each of the two test tasks in the baseline and the three post-TMS occasions. The three post-TMS RCSs were normalized with the RCSs for the baseline to adjust for participants' individual differences. The RCS can be interpreted as the number of correct responses per unit of time (Woltz and Was, 2006, p. 673) that addresses the potential speed-accuracy trade-offs with the following formula:

$$RCS_{i,j} = \frac{NC_{i,j}}{\sum_{K=1}^{n_{i,j}} RT_{i,j,k}}$$

where $NC_{i,j}$ is Participant *i*'s number of correct responses in Condition *j* and the denominator reflects the total time Participant *i* spent on trials in Condition *j* (in other words, the sum of RTs across all n_{ij} trials of Participant *i* in Condition *j*) (Liesefeld and Janczyk, 2019).

We then applied structural equation modeling (SEM) to compare the effects of the iTBS and CTBS on the participants' processing speed in the SRT and SDMT. Means and SDs of all variables used in the SEM were calculated and correlated with each other. The initial model, the iTBS vs SHAM model (M1), and the CTBS vs SHAM model (M2) were constructed. The data to model fit was evaluated using the Chi-squared (χ^2), comparative fit index (CFI), and the root mean square error of approximation (RMSEA) (Schermelleh-Engel et al., 2003). The criteria set for a significant and good data to model fit were $\chi^2/df < 2$, CFI > 0.97, and RMSEA <0.05, and an acceptable fit by $\chi^2/df < 3$, CFI > 0.95, and RMSEA <0.08 (Schermelleh-Engel et al., 2003).

3 Results

3.1 Characteristics of participants

There were no significant differences in age, gender, years of education, or Mini-Mental State Examination scores in the participants among the iTBS, CTBS, and SHAM groups (Table 1). All participants

TABLE 2 The results of the Group, Time, and Group × Time effects on the normalized RCS of the participants on the SRT and SDMT.

Tasks	Groups	Group effects p_a	Time effects p_b	Interaction effect p_c
SRT Normalized RCS	iTBS	0.241	**<0.001*****	0.669
	CTBS			
	SHAM			
SDMT Normalized RCS	iTBS	0.683	**<0.001*****	0.257
	CTBS			
	SHAM			

RCS, Rate-correct score; SRT, Simple reaction time; SDMT, Symbol digital modality test; ***$p \leq 0.001$, **$p \leq 0.05$. Bold values are measurement model.

completed the 5-day stimulation protocols and all the test tasks. Figure 2 shows the normalized RCS from the SRT and SDMT of participants in the three groups. RM-ANCOVA did not review significant Group × Time and Group effects on the normalized RCS of the SRT and SDMT (Table 2). The Time effect was statistically significant for the normalized RCS of the SRT [$F(2, 65) = 9.34$, $\eta^2 = 0.140$, $p < 0.001$] and SDMT [$F(2, 65) = 25.21$, $\eta^2 = 0.306$, $p < 0.001$]. The gender covariate was significant for the SRT [$F(1, 65) = 6.28$, $\eta^2 = 0.052$, $p = 0.014$] but not for the SDMT [$F(1, 65) = 1.50$, $\eta^2 = 0.013$, $p = 0.223$]. The baseline RCS covariate was not significant for the SRT [$F(1, 65) = 0.52$, $\eta^2 = 0.004$, $p = 0.472$] and SDMT [$F(1, 65) = 2.96$, $\eta^2 = 0.025$, $p = 0.087$].

3.2 The effects of stimulation on processing speed

3.2.1 The initial SEM model

The initial model was constructed to include the TMS, gender of participants, and normalized RCS factors (Figure 3). The first-order factors were the iTBS, CTBS, and SHAM conditions, as well as gender. The second-order factor was the reaction times of the SRT and SDMT, which were affected by the first-order factors. The third-order factors were the normalized RCSs of the SRT and SDMT in the three test occasions, i.e., post-TMS1, post-TMS3, and post-TMS5.

3.2.2 The iTBS (excitatory) vs SHAM effects on RpSMA

Supplementary appendix 3 summarizes the correlation patterns between the factor scores, mean scores, and standard deviation of the first-level and third-level factors. Furthermore, the "SRT_Post_TMS5" showed significant correlation with "SRT_Post_TMS3" ($r = 0.657$, $p < 0.001$), the "SDMT_Post_TMS3" showed significant correlation with "SDMT_Post_TMS1" and "SDMT_Post_TMS5" ($r = 0.809$, $p < 0.001$ and $r = 0.877$, $p < 0.001$, respectively), and the "SDMT_Post_TMS5" showed significant correlation with "SDMT_Post_TMS1" ($r = 0.798$, $p < 0.001$) (Supplementary appendix 3).

Supplementary appendix 4 summarizes the iTBS vs SHAM on RpSMA (M1) fitness indices for the SEM. The estimate of the structural model indicated that the "iTBSvsSHAM" to the latent factor "SRT_speed" path was found to be significant; of which the effects were direct and negative (standardized regression coefficient = −0.320, $p = 0.045$) (Figure 4; Table 3). In contrast, the "iTBSvsSHAM" to the latent factor "SDMT_speed" path was not statistically significant (standardized regression coefficient = 0.258, $p = 0.084$). All the "gender" originated paths and effects were not significant.

The loading of the measurement model indicated that the latent factor "SRT_speed" to "SRT_Post_TMS1," "SRT_Post_TMS3," and "SRT_Post_TMS5" paths were all significant, with standardized factor loadings ranging from 0.471 to 0.891 (all $p \leq 0.001$). All the other paths from the "SDMT_speed" to its subsequent SDMT reaction times were significant as well, which showed that the two latent variables "SRT_Speed" and "SDMT_Speed" can be well interpreted by three-level observative variables, respectively (Figure 4; Table 3).

3.2.3 The CTBS (inhibitory) vs SHAM effects on the MCV6

Supplementary appendix 5 summarizes the correlation patterns between the factor scores, mean scores, and standard deviation of the first-level and third-level factors. Furthermore, the "SRT_Post_TMS5" showed significant correlation with "SRT_Post_TMS3" ($r = 0.648$, $p < 0.001$), the "SDMT_Post_TMS3" showed significant correlation with "SDMT_Post_TMS1" and "SDMT_Post_TMS5" ($r = 0.766$, $p < 0.001$ and $r = 0.769$, $p < 0.001$), and the "SDMT_Post_TMS5" showed significant correlation with "SDMT_Post_TMS1" ($r = 0.776$, $p < 0.001$) (Supplementary appendix 5).

Supplementary appendix 6 summarizes the CTBS (inhibitory) vs SHAM on the MCV6 (M2) fitness indices for the SEM. The estimate of the structural model indicated that the "CTBSvsSHAM" to the "SRT_speed" latent factor path was found to be significant, of which the effects were direct and negative (standardized regression coefficient = −0.414, $p = 0.007$) (Figure 5; Table 4). In contrast, the "CTBSvsSHAM" to the "SDMT_speed" path was not statistically significant (standardized regression coefficient = 0.062, $p = 0.708$). All the "gender" originated paths and effects were not significant (Figure 5; Table 4).

The loading of the measurement model indicated that the latent factor "SRT_speed" to the "SRT_Post_TMS1," "SRT_Post_TMS3," and "SRT_Post_TMS5" factor paths were also significant, with the standardized factor loadings ranging from 0.509 to 0.822 (all $p \leq 0.001$). The "SDMT_speed" to its subsequent paths was significant as well, which showed that the two latent variables "SRT_Speed" and "SDMT_Speed" could be well interpreted by three-level observative variables, respectively (Figure 5; Table 4).

4 Discussion

This study aimed to test the roles of the RpSMA and MCV6 effective connectivity within the fronto-cerebellar network to subserve cognitive processing speed. The five-session TMS excitatory

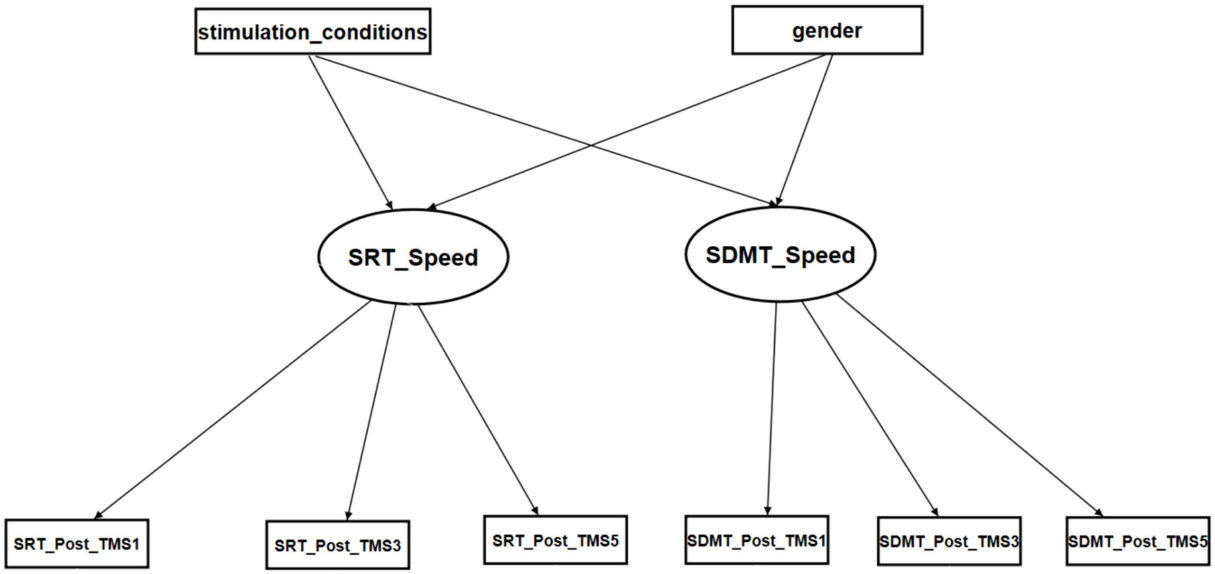

FIGURE 3
The initial SEM model for the reaction times of SRT and SDMT. Stimulation conditions: iTBS: 1, CTBS: 2, SHAM: 3. Gender: female: 0 and male: 1.

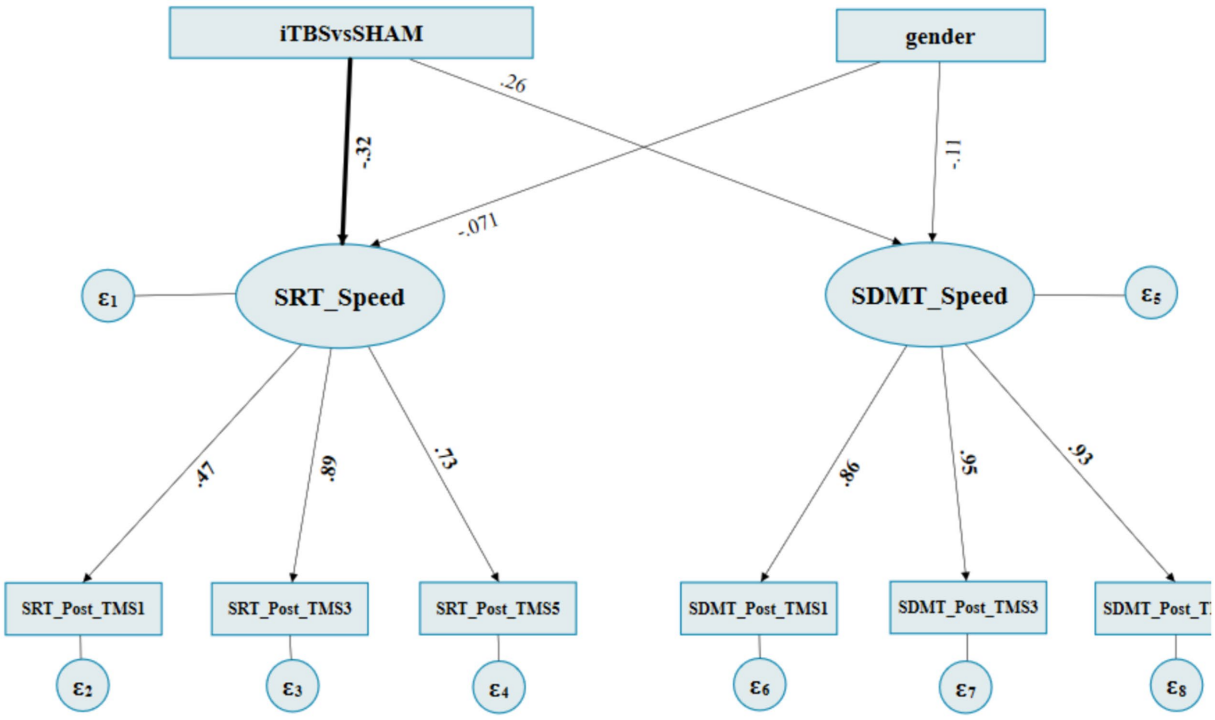

FIGURE 4
The final path diagram of SEM of iTBS vs SHAM on RpSMA. ITBS: 1, SHAM: 3. Gender: female: 0 and male: 1. SRT_Post_TMS1: SRT's normalized RCSs at post^{1st} occasion, SRT_post_TMS3: SRT's normalized RCSs at post^{3rd} occasion, SRT_Post_TMS5: SRT's normalized RCSs at post^{5th} occasion. SDMT Post_TMS1: SDMT's normalized RCSs at post^{1st} occasion, SDMT_post_TMS3: SDMT's normalized RCSs at post^{3rd} occasion, SDMT_Post_TMS5: SDMT's normalized RCSs at post^{5th} occasion.

and inhibitory protocols were intended to initiate changes in the participants' task-based reaction times. Despite the changes in the reaction times that had been observed across the stimulation sessions, they were at best regarded as marginal because they did not reach statistical significance. However, the results of structural equation modeling revealed systematic significant stimulation effects on both the RpSMA and MCV6, resulting in significant paths on the reaction time change factors. More importantly, the significant paths

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TABLE 3 SEM regression weights of iTBS vs SHAM on RpSMA.

Measured variables	Standardized regression coefficient	S.E.	95% C.I.	*p*-value
Estimate of structural model				
iTBSvsSHAM→SRT_speed	−0.320	0.160	[−0.634, −0.007]	**0.045****
iTBSvsSHAM→SDMT_speed	0.258	0.149	[−0.035, 0.551]	0.084
Gender→SRT_speed	−0.070	0.166	[−0.395, 0.254]	0.670
Gender→SDMT_speed	−0.105	0.155	[−0.409, 0.199]	0.498
Loading of measurement model				
SRT_speed→SRT_Post_TMS1	0.471	0.140	[0.196, 0.746]	**0.001*****
SRT_speed→SRT_Post_TMS3	0.891	0.119	[0.657, 1.126]	**<0.001*****
SRT_speed→SRT_Post_TMS5	0.732	0.117	[0.500, 0.962]	**<0.001*****
SDMT_speed→SDMT_Post_TMS1	0.856	0.048	[0.762, 0.951]	**<0.001*****
SDMT_speed→SDMT_Post_TMS3	0.946	0.031	[0.886, 1.007]	**<0.001*****
SDMT_speed→SDMT_Post_TMS5	0.926	0.034	[0.860, 0.993]	**<0.001*****

**$p \leq 0.05$; ***$p \leq 0.001$; S.E., standard error; 95% C.I., confidence interval. Bold values are measurement model.

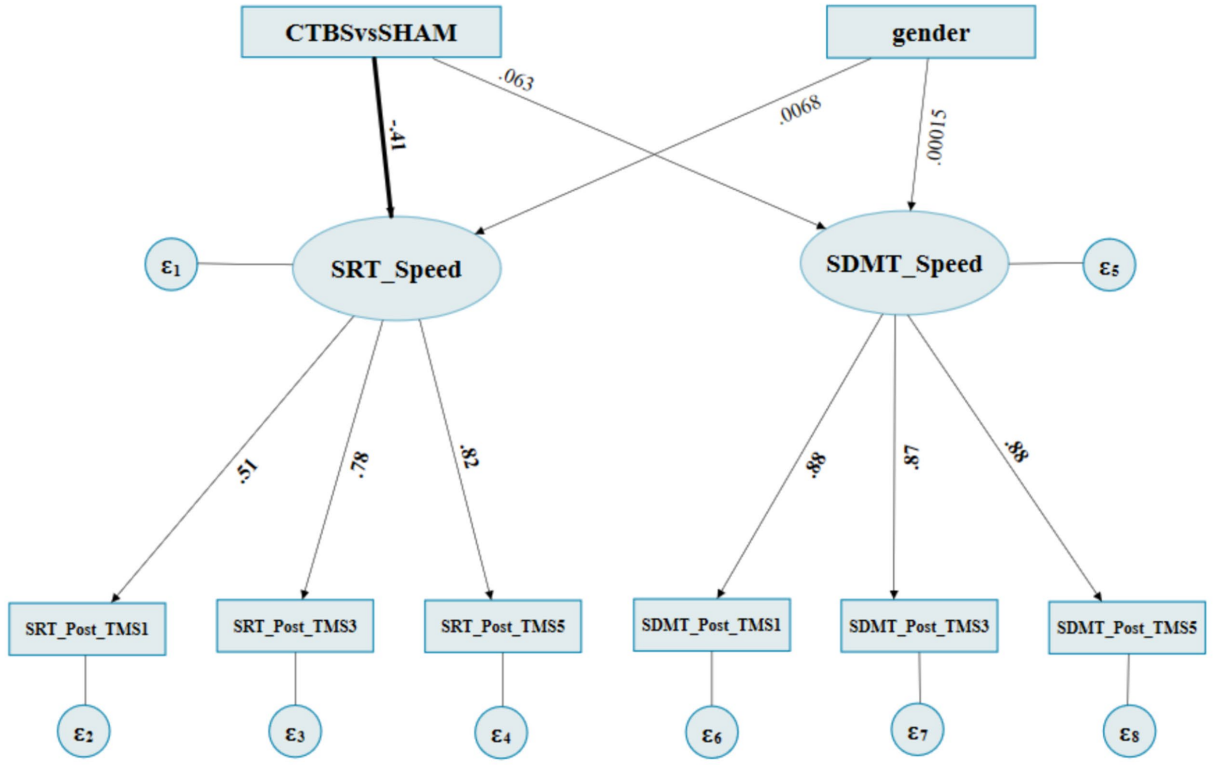

FIGURE 5
The final SEM path diagram of SEM of CTBS vs SHAM on MCV6. CTBS: 2, SHAM: 3. female: 0 and male: 1. SRT_Post_TMS1: SRT's normalized RCSs at post[1st] occasion, SRT_post_TMS3: SRT's normalized RCSs at post[3rd] occasion, SRT_Post_TMS5: SRT's normalized RCSs at post[5th] occasion. SDMT_Post_TMS1: SDMT's normalized RCSs at post[1st] occasion, SDMT_post_TMS3: SDMT's normalized RCSs at post[3rd] occasion, SDMT_Post_TMS5: SDMT's normalized RCSs at post[5th] occasion.

from the stimulation to the faster reaction time factors were only observed in the simple but not in the complex tasks. Excitation to the RpSMA relating to the faster reaction times in the simple task supports its "increase in the negative influence" role in the RpSMA➔MCV6 effective connectivity. Counterintuitively, inhibition of the MCV6 relating to the faster reaction times in the simple task did not support its unique role in the effective connective network to subserve processing speed. In other words, the iTBS protocol on the MCV6, which was supposed to reverse the "increase in the negative influence" originally received from the RpSMA, did

TABLE 4 SEM regression weights of CTBS vs SHAM on MCV6.

Measured variables	Standardized regression coefficient	S.E.	95% C.I.	*p*-value
Estimate of structural model				
CTBSvsSHAM→SRT_speed	−0.414	0.154	[−0.716, −0.113]	**0.007****
CTBSvsSHAM→SDMT_speed	0.062	0.167	[−0.265, 0.390]	0.708
Gender→SRT_speed	0.006	0.164	[−0.316, 0.330]	0.967
Gender→SDMT_speed	0.001	0.166	[−0.327, 0.327]	0.999
Loading of measurement model				
SRT_speed→SRT_Post_TMS1	0.509	0.149	[0.217, 0.801]	**0.001*****
SRT_speed→SRT_Post_TMS3	0.775	0.114	[0.551, 1.001]	**<0.001*****
SRT_speed→SRT_Post_TMS5	0.822	0.115	[0.595, 1.049]	**<0.001*****
SDMT_speed→SDMT_Post_TMS1	0.877	0.051	[0.776, 0.977]	**<0.001*****
SDMT_speed→SDMT_Post_TMS3	0.873	0.052	[0.771, 0.976]	**<0.001*****
SDMT_speed→SDMT_Post_TMS5	0.882	0.050	[0.784, 0.981]	**<0.001*****

**$p \leq 0.05$; ***$p \leq 0.001$; S.E., standard error; C.I., confident interval. Bold values are measurement model.

not produce slower reaction times. The contradictory results obtained from the MCV6 are plausibly due to the influences exerted by the available short-range connective networks within the cerebellum.

Excitatory stimulation on the RpSMA did not produce significantly faster reaction times when compared with the sham condition. The non-significant results were yielded from conducting conventional Group × Time comparisons. Our findings are consistent with those reported in two previous studies, reporting the effects of excitatory stimulations on the RpSMA. One study employed quadripulse transcranial magnetic stimulation over the pre-SMA, which did not produce significant effects on participants' performances in the simple choice reaction time task (Shimizu et al., 2020). Another study adopted a similar stimulation protocol to this study on the RpSMA, which showed significant modulation effects on the biceps brachii corticomotor excitability in individuals with tetraplegia (Mittal et al., 2022). However, several studies on similar topics involved excitatory stimulations applied to the dorsolateral prefrontal cortex. The results of these studies were largely equivocal on excitatory stimulations producing faster reaction times (Curtin et al., 2019; Song et al., 2020; Ngetich et al., 2022). Future studies can modify the stimulation protocols, such as increasing the dosage of the stimulation (intensity or duration) and enlarging the sample size. These strategies would increase the effect size of the stimulation, hence the chance of showing significant post-stimulation changes.

The results of the significant structural paths suggested the excitatory RpSMA effects related to faster post-stimulation reaction times in the simple, not complex task. The first level path was the excitatory RpSMA, which showed direct and negative effects on the latent simple task speed factor, while the second level path was the latent speed factor, which continued with similar relationships with the reaction times. The evidence renders support for Wong et al. (2021)'s proposition on the RpSMA "lowering negative influence" relationships with the MCV6 in the RpSMA➔MCV6 effective couple. The RpSMA or pre-SMA, part of the motor cortex, primarily relates to motor functions (motor inhibition, visuomotor sequence learning, the control of motor sequences, and modulation of the balancing of speed vs accuracy) (Georgiev et al., 2016; Obeso et al., 2017; Hanoğlu et al., 2020; Shimizu et al., 2020; Nakajima et al., 2022). One previous study reported that RpSMA subserved cognitive control such as response inhibition (Obeso et al., 2013). Our findings are contrary to those reported by Obeso et al., who showed that RpSMA was associated with simple rather than complex cognitive operations. The simple reaction time task employed in our study required the participants to decode symbols presented but make mono responses. The complex task was the symbol digit modalities task, requiring participants to decode, match, and respond according to the different symbol-digit pairs. In other words, the cognitive control processes would have been a part of the complex task but not part of the simple task. Future studies will need to replicate simple vs complex tasks to generate more robust results on the observed role of the RpSMA.

Similar to the RpSMA, inhibitory stimulation to the MCV6 did not produce significant changes in the participants' reaction times. Deliberation on the significant direct and negative paths from the inhibitory MCV6 to the latent speed factor only in the simple but not in the complex task sheds light on its role in the RpSMA➔MCV6 effective connectivity. The MCV6-induced latent speed factor showed significant direct and negative paths to the simple task reaction times. In other words, the inhibitory MCV6 related to faster rather than slower reaction times, which was inconsistent with the study's hypothesis. One plausible explanation for the contradictory results could be that the inhibitory stimulation was over-spilled to other cerebellar sites. Two studies reported inhibitory stimulations resulting in faster reaction times involving sites different from the MCV6. They were the stimulation at the 1–2 cm below the inion (adjacent to MCV6) (Heleven et al., 2021) or the right Crus I/Crus II (adjacent to MCV6) (Gatti et al., 2020). Both studies revealed significantly faster reaction times in complex tasks: picture sequencing (Heleven et al., 2021) or word pairing (Gatti et al., 2020). These studies further explained that inhibitory stimulation possibly would have modulated the inherent sequence processing, semantic function in language, or semantic memory function required in the complex tasks. The over-spilled inhibition speculation does not seem to offer insight into the

counterintuitive findings. Another plausible line of explanation is from a recent study that applied inhibitory stimulation over the left cerebellum (1 cm below and 3 cm lateral to the inion), resulting in faster reaction times in a lexical decision task (Allen-Walker et al., 2018). Allen-Walker et al. attributed the faster reaction time to activate the automatic and fast feedback loops in the left cerebellar hemisphere after CTBS was applied with the left cerebellum or contralateral cerebral cortex (right temporal cortex) as a result of left cerebellar rTMS. An earlier study using the same lexical decision task and applying inhibitory stimulation to the site similar to MCV6 revealed deterioration of reaction times (Argyropoulos, 2011). Argyropoulos (2011) explained that the participants' deteriorated performance could have been attributable to disrupted oculomotor processes by the inhibitory MCV6 essential for the reading during the task (Argyropoulos, 2011). Their argument was supported by a later study suggesting that the cerebellar stimulation could have modulated the primary motor cortex via the efferent path of the fronto-pontine-cerebello-thalamo-cortical loop (Grimaldi et al., 2014). However, the fronto-pontine-cerebello-thalamo-cortical loop is different from the fronto-cerebellar network, which contains the RpSMA➔MCV6 in this study. The latter is a long-range connectivity between the frontal cortex and the cerebellum without the dentate and motor thalamus (Wong et al., 2021). The lexical decision task involved semantic processing and higher cortical function, which is different from the simple reaction task in this study. Taken together, the inhibitory effects on the cerebellum are likely to vary with the location of stimulation and the content of the tasks. Future studies would explore the mechanism of combined existing connectivity or new models for the roles of the cerebellum in subserving cognitive processing speed.

A plausible explanation of the inhibitory MCV6 for the RpSMA➔MCV6 may be explained by the long- and short-range fronto-cerebellar effective connectivity revealed in our previous study (Wong et al., 2021). Long-range cerebellar connectivity plays a dominant role in subserving cognitive information processing (Deco et al., 2021). The RpSMA➔MCV6 couple is long-range connectivity. In the same study, Wong et al. revealed MCV6➔RCH6, a short-range connectivity, in which the MCV6 exerted a lower positive influence on the RCH6, predicting faster processing speed (Wong et al., 2021). Functional connectivity within the cerebellar networks was suggested to be associated with learning in young adults (Edde et al., 2020). The effect of RpSMA➔MCV6 on processing speed was found to be independent of that of MCV6➔RCH6 (Wong et al., 2021). We, therefore, speculate that the opposite effects manifested from the inhibitory MCV6 could have been intervened by the short-range cerebellar connectivity, such as the RCH6. However, the effect of short-range connectivity is outside the scope of this study. Further study should include both long- and short-range connectivities in building a comprehensive model for the cerebellum.

Another finding revealed in this study is stimulations at the RpSMA, and MCV6 showed effects on the simple but not complex tasks. These findings perhaps would have been confounded by the RpSMA➔MCV6 effective connectivity reported by Wong et al. (2021), which was based on the modified arrow test, which involved relatively simple cognitive operations. The simple reaction time task deployed in this study required basic information processes, such as encoding and discrimination of the figure "0," and a one-to-one task rule of "press on a key" when seeing "0" (Deary et al., 2010). Our findings are consistent with an earlier study that a simple reaction time task involved activations of the premotor cortex, medial frontal gyrus, cerebellar vermis, and frontal–parietal cortex, which overlaps with the RpSMA and MCV6 (Kansaku et al., 2004). On the contrary, studies that employed more complex tasks, such as the SDMT deployed in this study, have been found to activate the other brain regions, including the frontal–parietal cortex, cingulate gyrus, and precuneus (Silva et al., 2018).

4.1 Limitations and future perspectives

There are a few limitations in this study. First, the simple task reaction time results are likely to be confounded by the modified arrow test, which involves relatively simple cognitive operations. Second, we adopted single and separate rather than multiple and simultaneous protocols over RpSMA and MCV6 for testing the RpSMA➔MCV6. The single and separate site stimulation could have weakened the effects modulating the fronto-cerebellar connective network. The non-significant modulating effects for the complex task performance could have been due to the five-session protocols producing inadequate stimulation effects or the ceiling effect among the young, healthy participants. The task choices in our study were only limited to simple and complex tasks in their relativity, which do not represent the wide spectrum of cognitive operations. Finally, the study's sample size was relatively small, which could have weakened the power to detect any possibly significant changes, particularly in the complex task's performances. Future studies should replicate the study with a large sample size and adopt more stimulation conditions, such as dual-site simultaneous protocol, increasing the dosage of the stimulation, and more cognitive tasks with different mental operations. The validity of the stimulation to modulate the fronto-cerebellar network would need to go beyond a behavioral study, such as a brain imaging method, to quantify the post-stimulation functional changes within the network. The young, healthy participants of this study limit the generalization of the findings to other healthy age groups and diagnostic groups. Readers should interpret the results with caution.

5 Conclusion

We attempted to understand the role of the individual neural substrates in the RpSMA➔MCV6 effective connective couple within the fronto-cerebellar network. The hypotheses set for the study were partly supported. Based on the structural equation modeling results, excitatory stimulation at the RpSMA showed significant paths to faster reaction times in the simple cognitive task. The results supported the RpSMA playing a lower negative effect role, as proposed in our previous study inhibiting the MCV6, which subserves faster processing speed. However, the results from the inhibitory MCV6 showed that significant paths to the faster reaction times in the simple cognitive tasks did not support the hypothesis. The anticipated inhibition of the MCV6, which was supposed to be associated with slower reaction times, could have been compromised by the short-range cerebellar connectivity, such as the RCH6.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Rehabilitation Hospital affiliated with the Fujian University of Traditional Chinese Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

NZ: Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing, Visualization. JT: Project administration, Software, Supervision, Writing – review & editing, Investigation. CW: Methodology, Software, Writing – review & editing. JW: Methodology, Software, Writing – review & editing. JL: Methodology, Software, Writing – review & editing. LC: Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing, Methodology. TL: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. YX: Writing – review & editing. CC: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2024.1387299/full#supplementary-material

SUPPLEMENTARY APPENDIX 1
Task design of simple reaction time task (SRT).

SUPPLEMENTARY APPENDIX 2
Task design of SDMT.

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Research progress on the intervention of cognitive function using transcranial alternating current stimulation technology

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Transcranial Alternating Current Stimulation (tACS) is a non-invasive brain stimulation that stimulates the cerebral cortex through the output current to regulate neural excitability. This review systematically summarizes the research results of tACS on working memory, learning ability, and decision-making ability, and analyzes the application schemes, safety, and unresolved issues of tACS in the field of cognitive function to provide a theoretical reference for the application of tACS in the field of cognition. Research has found that: (1) tACS intervention can improve the working memory, learning ability, and exercise decision-making ability of athletes and healthy individuals and has a positive effect on improving exercise performance. (2) The factors that determine the effectiveness of tACS intervention include stimulation frequency, stimulation phase, stimulation area, and stimulation dose. The stimulation area and frequency determine which cognitive function tACS affects, whereas the stimulation phase and dose determine the magnitude of the intervention effect. Moreover, before practical application, individual cognitive status, age level, and timing of application should be included in the factors that affect the effectiveness of tACS intervention to develop more scientific intervention plans. (3) Despite the absence of evidence indicating significant safety issues associated with the use of tACS, its widespread adoption among athletes still poses safety risks under the World Anti-Doping Code. In competitive sports, whether the use of tACS will be classified as a "neuro-doping" method leading to disqualification remains uncertain. Therefore, authoritative institutions to provide comprehensive guidelines on the application of tACS, clearly delineating its usage scenarios and defining the safety parameters for tACS stimulation. Additionally, the development of detection devices for tACS usage is essential to ensure that any intervention using tACS can be monitored effectively.

KEYWORDS

transcranial alternating current stimulation, cognitive function, intervention effects, application strategies, ethical

1 Introduction

The brain is the foundation of human movement and cognition, playing a crucial role in improving motor performance and cognitive function (Wu et al., 2021). In recent years, the relationship between sports performance and cognitive function has received much attention, and advances in neuroscience have made it possible to explore the relationship between motor performance and cognitive function (Yin et al., 2014). The improvement

of cognitive function often promotes good motor performance, which has been confirmed by many studies (Hockey, 1993; Cao, 2016; Zhao et al., 2021; Tod et al., 2015; Kamali et al., 2019). At present, brain neural regulation technology is an important means to improve cognitive function in the brain. Transcranial Electrical Stimulation (TES) is a non-invasive brain neural regulation technology that activates cortical neurons to improve cognitive function by stimulating electrodes to apply low-intensity currents to specific brain regions. TES can be divided into transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) based on different current forms. Among them, tDCS has achieved good results in the fields of exercise and rehabilitation, improving the exercise performance of users. Unlike tDCS, tACS can induce more persistent synaptic changes through frequency oscillations and peak time plasticity, resulting in a longer duration of action of tACS (Kasten and Herrmann, 2017). And because the stimulation of tACS is bipolar current, the side effects of tACS are smaller, which has attracted the interest of many researchers (Antal et al., 2017).

Cognitive function is a complex brain activity encompassing working memory, learning ability, motor decision-making, and visuospatial skills (Ren et al., 2013; Fresnoza et al., 2020; Hwang et al., 2022). In actual sports activities, not only is physical participation required, but cognitive involvement is also necessary. The more complex the sports scenario, the deeper the cognitive involvement needed, often requiring more cognitive resources to handle changes in the sports situation, such as analyzing action techniques and sports scenarios, and making decisions under pressure. These factors collectively increase the cognitive load on athletes, including working memory and motor decision-making (Borson, 2010). Prolonged cognitive engagement can lead to cognitive fatigue, where excessive energy consumption by the brain results in a temporary decline in cognitive performance. This decline can adversely affect sports performance, reduce competition results, and even cause sports injuries (Holtzer et al., 2011; Van Cutsem et al., 2017). Research has found that working memory, learning ability, and sports decision-making are closely related to sports performance, with almost every type of sport involving these three cognitions (Tang et al., 2020; Zhu et al., 2015). Furley et al. found in their research that the improvement of sports performance depends on working memory, decision-making, skill acquisition, sensory perception, and stress (Furley et al., 2010). Working memory is the foundation of other higher-lever cognitive functions, and almost all cognitive functions are based on working memory, such as motor learning and motor decision-making. In the process of mastering motor skills, the stronger the working memory ability and motor learning ability, the faster the speed of mastering sport skills, the higher the degree of sport automation, and the better the sport performance (Zhou et al., 2018; Kal et al., 2016). For sports competitions with complex sports scenarios, higher-level motor decision-making is needed to improve their performance. Excellent athletes are usually able to make quick decisions to adapt to changes in the competition more quickly. Accurate decision-making can reduce the chances of errors, help athletes effectively execute tactics and strategies, and also effectively leverage their technical and physical advantages to improve their sports performance and improve competition results (Amann and Secher, 2010; Huijgen et al., 2015; Head et al., 2017). Moreover, these three cognitive functions have certain similarities in the functional areas of the brain, involving most areas of the brain, and the main functional areas are in the frontal and parietal lobes (Smith and Jonides, 1999; Meissner et al., 2018; Gaudry and Kristan, 2012). tACS has increasingly been used as a neuroregulatory technique to modulate cognitive abilities, even becoming a crucial means to enhance cognition (Tavakoli and Yun, 2017). However, the current application effects of tACS in the cognitive domain are mixed, necessitating scientific application paradigms to guide the use of tACS in the cognitive field to improve sports performance.

Based on the above reality, this study summarizes the relevant research on tACS intervention on working memory, motor learning, and motor decision-making in the past 30 years, analyzes the effect of tACS on the above cognitive functions, summarizes the practical application plans and safety issues of tACS, and provides theoretical basis and application guidance for the application of tACS in the cognitive field of athletes, to help athletes, coaches, and researchers better utilize tACS to participate in sports training and competitions.

2 Overview of transcranial alternating current stimulation

2.1 Definition and parameters

tACS stimulates the cerebral cortex by outputting sinusoidal alternating currents of different frequencies, where the voltage gradually changes from positive to negative every half cycle. Therefore, the current flows from the anode electrode to the cathode electrode within one and a half cycles, and in the second half cycle, it flows in the opposite direction (Ruffini et al., 2013). Clinically, different frequencies of current are commonly used to regulate brain oscillations and induce brain function (Antal and Paulus, 2013). At present, the common stimulation frequencies of tACS include 6.5, 10, 20, 40, 50, and 70 Hz, etc. The duration of current stimulation is mostly between 20 and 30 min, and the area of the stimulation electrode is 16, 25, and 35 cm^2. The peak-to-peak intensity of current stimulation is generally between 0.5 mA and 2 MA (Klink et al., 2020).

2.2 Physiological mechanisms

tACS stimulates the cerebral cortex through sinusoidal alternating current, and its mechanism of action can be divided into the following: ① exogenous oscillations induce endogenous oscillations in the brain; ② Inducing synaptic plasticity to regulate brain function; tACS regulates endogenous brain oscillations in a frequency-specific manner by applying a specific frequency of current to the cerebral cortex, altering the membrane potential of dendrites or axons in an oscillatory manner. This oscillation can interact with natural oscillations in the distant cerebral cortex, ultimately triggering the excitation of brain neurons. tACS can emit current frequencies related to cognitive function, thereby affecting

cognitive ability Applying tACS stimulation slightly higher or lower than the intrinsic frequency of brain regions can accelerate or decelerate intrinsic oscillations (Vöröslakos et al., 2018; Raco et al., 2014).

3 Research progress on improving cognitive function through transcranial alternating current stimulation

In recent years, tACS has received more attention due to its AC characteristics and safety. Some research on tACS has mostly focused on promoting motor skills and cognitive regulation (Zhang and Lv, 2024; Li et al., 2023; Zhang and Li, 2022). Scholars Qian et al. pointed out that cognitive functions mainly include attention, working memory, executive power, decision-making power, and multitasking ability (Qian et al., 2020). Klink et al.'s research found that working memory, motor learning, and decision-making power are highly correlated with motor performance (Klink et al., 2020), which is one of the prerequisites affecting motor performance. The complexity of cognitive function is high, and individual differences are significant (Shaw et al., 2020; Lövdén et al., 2020). Therefore, when using tACS to intervene in cognitive function, the results often have differences. This review reveals the effects of tACS on different cognitive functions, summarizes the application plans of transcranial alternating current, and provides a reference for the application of tACS in the cognitive field.

3.1 Impact of transcranial alternating current on working memory

This study found that tACS can improve working memory in healthy individuals (Bender et al., 2019). However, the selection of frequency has specificity. Compared with a frequency of 7 Hz, a frequency of 4 Hz can better improve working memory levels. The reason is that the effect of tACS on working memory propagates along the brain network. When the induced frequency emitted by tACS matches the endogenous rhythm, the entrainment effect is better. And theta oscillation acts as a gating mechanism in working memory, providing optimal neural conditions for specific processing (Jaušovec et al., 2014) found that the oscillation frequency of 4 Hz is closer to that of the human brain theta frequency, therefore, a 4 Hz frequency has a significant impact on an individual's working memory. Scholar Borghini et al. analyzed from the perspective of θ-γ phase coupling theory and believed that slower theta waves (4 Hz) allow more gamma cycles to be nested within slower theta waves (4 Hz) compared to faster theta waves (7 Hz), thereby improving working memory capacity (Borghini et al., 2018). Scholar Sauseng et al. also supports this viewpoint and believes that multiple gamma wavebands can be nested within theta frequency band, it can promote instantaneous memory of multiple items, ultimately increasing working memory capacity (Sauseng et al., 2019). Roux and Santarnecchi found in their study that when cognitive load capacity is high, the stimulation effect of gamma band tACS is more significant. Although γ-tACS has a positive impact on improving working memory, the improvement effect also varies. When cognitive load is higher, tACS prioritizes improving performance in more complex cognitive tasks. Santarnecchi and colleagues found in their research that in complex tasks γ- tACS stimulation first improves accuracy in working memory rather than reflecting time (Santarnecchi et al., 2013). Hoy et al.'s study is similar to the above. When Hoy used γ-tACS to stimulate the F3 region, she found that it did not improve overall working memory performance, nor did it have a significant effect on improving task response time, but it could incresae higher working memory loads (Hoy et al., 2015).

At present, the relationship between the stimulation effect of gamma band tACS and the state of the brain when stimulated is not clear. Most scholars believe that the effect of tACS stimulation on working memory is influenced by the state of the brain at that time. When the brain is in a state of high cognitive load, the stimulation effect of gamma band is significant, but ceiling effect is prone to occur (Hoy et al., 2015; Roux et al., 2012). High working memory demands are typically associated with high-level frontal parietal connections, and synchronous tACS stimulation can enhance the entire brain network, thereby improving working memory levels (Violante et al., 2017). Some scholars also believe that the effect of tACS on working memory is correlated with the level of cognitive task participation (Polanía et al., 2012), and the deeper the level of cognitive participation, the greater the effect of tACS. Some scholars also believe that the effect of tACS stimulation is more likely to manifest only in individuals with poor working memory performance (Tseng et al., 2018).

In summary, this study indicates that the frequency of the impact of tACS on working memory is mainly concentrated in theta and gamma within the frequency band, and the stimulation area is mainly in the frontal and parietal lobes. When working memory performance is poor, the intervention effect of θ-tACS is better. When working memory is under high cognitive load, the intervention effect of γ-tACS is better, and the main improvement is the accuracy of working memory (Table 1).

3.2 Impact of transcranial alternating current on learning ability

This study found that tACS can regulate neural activity through oscillating currents and improve the performance of motor learning. The synchronous oscillation activity at frequencies alpha (8–12 Hz) and beta (13–30 Hz) is believed to promote neuronal plasticity, thereby improving motor learning ability.

Pollok et al. found that tACS stimulation in the alpha frequency band (10 Hz) has a positive effect on learning motor sequences, and only when stimulating the parietal lobe can its effect be exerted. This is similar to the previous research results of Antal, in which Antal et al. found that tACS stimulation at 10 Hz has a significant promoting effect on implicit motor sequence learning (Pollok et al., 2015; Antal et al., 2008). Further research has found that tACS stimulation in the beta band (20 Hz) has a positive effect on learning stability and is less sensitive to interference. This is similar to Antal et al.'s previous research, in which Antal found that tACS

References	Research object	Electrode position	Frequency (Hz)	Time (min)	Intensity (mA)	Electrode size	Cognition task	Effect of action
Jaušovec and Jaušovec (2014)	36 healthy adults with an average age of 20 ± 4.25 years old	Left parietal cortex (P3)+supraorbital frontal cortex (F3); Right parietal cortex (P4)+supraorbital region	ITF	15	1–2.25 (pp)	(5*5) cm^2	N-back task memory task	Significantly improved working memory performance
Violante et al. (2017)	24 healthy adults, 27.38 ± 4.56 years old	Frontal/parietal region (F4/P4), T8 F4, and P4, T8	6	20	1 (pp)	(5*5) cm^2	2-back/1-back and selective reactions	Improving speech working memory performance
Wolinski et al. (2018)	Group 1 has an average age of 28.3 ± 7.6, Group 2 has an average age of 22.8 ± 5.2, and each group has 16 people	Parietal cortex (P4)+vertex (Cz)	4, 7	12	1.24 ± 0.3 mA	(5*5) cm^2	Working memory task	4 Hz increases the working memory capacity, while 7 Hz reduces the shared working memory capacity.
Zeng et al. (2022)	36 healthy adults with an average age of 23.67 ± 1.97	FP1-AP7, FP2-AF8	4, 8, sham	20	2 (pp)	(4.5*5.5) cm^2	N-back task memory task	8 Hz can improve performance in verbal n-back tasks
Pahor and Jaušovec (2018)	72 healthy female students with an average age of 20.38 ± 1.48	Group 1:P3-P4, Group 2:F3-P3, Group 3:F4-P4, Group 4:F3-F4	Group 1: θ4.94, γ31.81; Group 2: θ4.89, γ33.22 Group 2: θ5.08, γ32.60 Group 4: θ5.28	15	2 (pp)	(7*5) cm^2	N-back task memory task	θ-tACS stimulation in the posterior parietal lobe enhances working memory
Zhang et al. (2022)	20 healthy young participants with an average age of 22.45 ± 2.52	F4, P4	6	15	2(pp)	(5*5) cm^2	N-back task memory task	6 Hz stimulation has no significant effect on low-load working memory

ITF represents an individual θ Frequency; Pp represents the peak-to-peak value of the current; Sham represents false stimulation.

TABLE 2 The effect of transcranial alternating current stimulation on learning ability.

References	Research object	Electrode position	Frequency (Hz)	Time (min)	Intensity (mA)	Electrode size	Cognition task	Effect of action
Nguyen et al. (2018)	30 healthy individuals with an average age of 24 years old	MFC and Right LPFC	6	20	1(pp)	NG	Time estimation task	Improved learning ability
Pollok et al. (2015)	13 healthy individuals with an average age of 22.08 years	Left M1 and above the right eye socket	10, 20, 35 and shame	12 min 12 s	1(pp)	(5*7) cm^2	SRTT	10 and 20 Hz tACS promote learning of motion sequences
Miyaguchi et al. (2018)	30 healthy individuals with an average age of 21 ± 0.36 years	Right M1, left cerebellar cortex area	70	(60*8)S, 2 min apart each time	1 (pp)	(5*5) cm^2	Visual motion control tasks	The error rate of sports learning is significantly reduced
Wischnewski et al. (2016)	50 healthy individuals with an average age of 24.1 ± 7.80 years old	At the frontal cortex between F3 and Fc5, and between F4 and Fc6	6	11	1 (pp)	(5*7) cm^2	Reverse learning tasks	Reverse learning speeds up
Zhang et al. (2022)	14 healthy individuals with an average age of 22.53 ± 0 56 years old	Left M1 and above the right eye socket	20, 70 and sham	11	2 (pp)	(5*5) cm^2	SRTT	Both 20 and 70 Hz can improve motor skills and sequence response skills, and the effect of 70 Hz is more significant
Antal et al. (2008)	16 healthy individuals with an average age of 22.4 ± 4.15 years old	Left M1 and above the right eye socket	1, 10, 15, 30, 45, and sham	5	0.4(pp)	(4*5) cm^2 and (5*10) cm^2	SRTT	10 Hz tACS can shorten reaction time and improve implicit motion learning
Minpeng et al. (2019)	60 healthy individuals with an average age of 20–25 years old	Left and right primary motor cortex, ipsilateral supraorbital region	20	15	Sensory stimulus intensity	(5*5) cm^2	SRTT	Improved motor learning ability and shortened reaction time

FDI represents the first interosseous dorsal muscle; SRTT represents the sequence reaction time task; The intensity of sensory stimulation starts at 20 μ Step A increases the amplitude of the current, and when the subject has a slight pricking sensation or visual hallucinations on the scalp, increase it by 20 μ The step size of A decreases until the stimulus current disappears in the subject's sensation.

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stimulation at 10 Hz has a significant promoting effect on implicit motor sequence learning (Pollok et al., 2015; Antal et al., 2008).

Miyaguchi et al. (2018) found that tACS stimulation in the gamma band (70 Hz) can also improve the retention ability of motor learning by stimulating the M1 and cerebellar cortical areas, and the effect lasts for up to 24 h. This may be because tACS stimulation in the gamma band strengthens the neural network between M1 and the cerebellar hemisphere, and the neural network between M1 and the cerebellum is involved in monitoring motor errors and correcting motor planning, which is crucial for motor learning. Moreover, during motor preparation and execution, the gamma band activity in the M1 region increases, promoting information transmission in the sensory motor integration process (Pollok et al., 2015; Antal et al., 2008). During exercise tasks, the activity of the beta and gamma bands at M1 mutually inhibits each other. The application of γ-tACS on M1 may increase the activity of the gamma band while suppressing the activity of the beta band. This may be one of the reasons why gamma tACS (70 Hz) stimulation only improves the ability to maintain motor learning, which is consistent with the cross theory proposed by Pahor and Jaušovec (2014). Zhang et al. conducted experiments from the perspective of consolidating motor skills, and the results also support this conclusion. Research has found that within the same time window, compared to low-frequency (20 Hz) stimuli, high-frequency (70 Hz) stimuli have a greater effect and longer duration. Zhang et al. believes that when 70 Hz tACS stimulated the M1 region, **γ**-tACS increased brain gamma band activity and inhibited beta band activity, causing neurons related to motor learning and memory to be repeatedly stimulated by tACS, thereby promoting enhanced motor learning (Zhang et al., 2022). Actually, tACS stimulation in the alpha, beta, and gamma bands can all enhance motor learning ability. Pollok colleagues found that tACS stimulation at 10, 20, and 35 Hz can all improve motor learning ability. Compared to 10 and 20 Hz, the effect of 35 Hz is weaker. The reason why Pollok's research results differ from other scholars may be that Pollok places the stimulation position of tACS in the cortical layer of the first interfemoral muscle, while the experimental paradigm of motor learning ability is achieved through finger tapping on the keyboard. tACS intervention can provide strong stimulation to the cortical layer, and improve finger flexibility, and therefore all three stimulation frequencies can improve motor learning ability (Pollok et al., 2015). However, 20 Hz has the best effect on improving motor learning ability and has good anti-interference ability. Unlike the above, in Antal et al.'s study, 15 and 30 Hz tACS stimulation did not affect learning motor sequences, which may be due to the endogenous oscillatory state of the subject's brain, resulting in differences in effects between different studies (Antal et al., 2008). John Nguyen et al.'s study showed that when HD-tACS was applied to the medial frontal cortex (MFC) and lateral prefrontal cortex (lPFC) of subjects with open eyes, their learning ability was significantly improved. Further research has found that when subjects close their eyes, applying the same stimulation in the same position does not improve their learning ability (Nguyen et al., 2018). The reason may be that eye-opening behavior affects the neural network, leading to synchronization of the active theta band in the frontal lobe, thereby promoting functional connectivity between MFC and lPFC. This change is crucial for completing learning tasks, further proving that the endogenous oscillatory state of the subject's brain is an important factor affecting the effectiveness of tACS intervention.

In summary, the evidence provided in this study indicates that the brain regions that enhance motor learning ability are mostly selected as M1 or frontal cortex. alpha, beta, gamma band tACS stimulation has a positive effect on motor learning; θ-tACS on the frontal cortex improves rule learning ability, but at the same time interferes with the application of learning rules; β-tACS has the most stable effect on motor learning; The effect of γ-tACS on motor learning has a longer time effect, however, the endogenous oscillation state of the subject's brain can also affect the intervention effect (Wischnewski et al., 2016; Table 2).

3.3 Impact of transcranial alternating current on decision-making ability

This study found that tACS stimulation of the frontal lobe brain area can improve sport decision-making ability. Sela et al. used balloons to simulate risk tasks, stimulating the left and right prefrontal cortex separately. One group received stimulation in the right prefrontal cortex (rPFC), and tACS stimulation was performed 5 min before the start of the task until BART was completed. The stimulation frequency of tACS was 6.5 Hz, and the final results showed that tACS was stimulated in the left prefrontal cortex (lPFC) theta frequency band neural oscillations can improve the ability of motor decision-making and prompt subjects to take action (Feurra et al., 2012). The research results of Dantas et al. are different from the above. When Dantas applies θ-tACS stimulation to the left prefrontal lobe, their risky decision-making behavior decreases, the reason may be that the experimental paradigms of the two are different. Dantas's experimental paradigm is a gambling task, which avoids the impulses of loss and disgust. Marco discovered the correspondence between the frontal striatum and hippocampus through his study of EEG-fMRI, demonstrating that tACS stimulation may increase decision-making motivation by indirectly affecting brain regions of the reward system (Dantas et al., 2021). More importantly, the ventral striatum is a key subcortical area for risk decision-making, and its activation indicates the making of risk decisions, making it more likely to be activated as rewards increase (Niv et al., 2012). The study by Yaple et al. supports this viewpoint that when Yaple uses different frequencies of tACS to stimulate the frontal area, a 20 Hz left frontal lobe stimulation can significantly increase the motivation for risk decision-making. This may be because a 20 Hz stimulation may increase cortical excitability in the left frontal lobe region by driving the frontal striatal network, which can enhance the motivation for risk decision-making (Yaple et al., 2017).

The decision-making process involves multiple brain regions, including the frontal lobe, parietal lobe, insula, caudate nucleus, amygdala, and anterior cingulate gyrus. The frontal lobe plays a significant role in decision-making (Gold and Shadlen, 2007). Rao et al. demonstrated a link between the PFC and the decision to voluntarily accept greater risk, suggesting that the PFC in the prefrontal cortex is more closely related to accepting greater risk

References	Research object	Electrode position	Frequency (Hz)	Time (min)	Intensity (mA)	Electrode size	Cognition task	Effect of action
Sela et al. (2012)	27 healthy individuals with an average age of 23.89 ± 2 45 years old	Group 1: DLPFC(F3), (CP5), Group 2: DLPFC(F4), (CP6)	6.5	15	0.5 (pp)	(5 cm × 5) cm^2	BART	Stimulation of the right frontal lobe reduces motivation for risk decision-making behavior
Yaple et al. (2017)	Group 1: 17 healthy individuals with an average age of 20.52 ± 2.52 years old; Group 2: 17 healthy individuals with an average age of 21.17 ± 2.78 years old	Group 1: F3, ipsilateral deltoid muscle; Group 2: F4, ipsilateral deltoid muscle	5 10 20 40	40	0.5 (pp)	(5 cm × 7) cm^2	Risk Decision Tasks for Voluntary Conversion Tasks	20 Hz excitation of the left prefrontal cortex increases motivation for risk decision-making
Wischnewski et al. (2016)	18 healthy individuals with an average age of 21.9 ± 2.3 years old	Left and right prefrontal cortex; AF3 and AF4 outer 2cm, Fc1 and Fc2 outer 1 cm	5	30	0.5 (pp)	(3 cm × 5) cm^2	Modified version of sequential gambling task	Frontal lobe θ-tACS can increase the perception of uncertainty in adventure missions
Dantas et al. (2021)	31 healthy adults with an average age of 23.8 ± 3.45	The large electrode is on the left DLPFC, and the small electrode is on F3	Shame, 6.5, 40	30	0.5 (pp)	Electrode with a diameter of 2.1 cm and a circular ring with an outer diameter of 11 cm and an inner diameter of 9 cm	Cambridge Gambling Mission	6.5 Hz reduces motivation for adventurous behavior

BART represents balloon simulation risk task.

and that the PFC regulates the active volitional control of risk recipients by executing control parts (Rao et al., 2008). Further research has found that in decision-making contexts, right PFC activation is considered withdrawal decision-making behavior, while left PFC activation promotes decision-making behavior (Davidson, 2014). Student's research results differ from the above, as he found that compared to the left prefrontal cortex, the right prefrontal cortex (rPFC) has a higher theta Power (4–8 Hz), higher frontal theta band asymmetry, and more adventurous behavior in decision-making tasks (Studer et al., 2013). The reason may be that there are differences in the resting state of the individual's frontal lobe, which can affect one of the key factors in decision-making behavior. Therefore, when using tACS for intervention, the first step should be to conduct EEG testing to exclude individual differences in the resting state of frontal lobe asymmetry (Slovic, 1966).

In summary, this study indicates that the stimulation of the left frontal lobe by tACS is an important area for improving decision-making ability, and the theta frequency band is an important frequency band for stimulating frontal lobe activation. However, the asymmetry of the frontal lobe and differences in resting state are also factors that affect decision-making behavior (Table 3).

4 Impact of cognitive function on sports performance

4.1 Impact of working memory on sports performance

Working memory is the ability to temporarily store, acquire, and process information in the brain in order to achieve higher-level cognitive functions. It is the foundation of learning and decision-making abilities, and all sports skills and performance develop based on working memory (Ren et al., 2013). Therefore, working memory is crucial for movement. The frontal and parietal lobes are the main functional areas of working memory tasks (Palva et al., 2010). The executive function is related to the frontal lobe, while the storage of working memory is related to the parietal lobe (Champod and Petrides, 2010). When individuals perform complex tasks, the storage capacity of working memory is crucial for task performance, such as basketball and football; for easier tasks, control is dominant, such as high jump and long jump (Jaušovec et al., 2014).

In competitive sports, phenomena related to working memory, such as choking and stereotype threat, can affect sports performance (Hardy et al., 1996). The phenomenon of choking consumes cognitive resources, reducing working memory capacity and impairing athletic performance. Stereotypes are similar to choking, which can cause individuals to refocus on well-practiced sensorimotor skills, interfering with their automatic execution and reducing working memory capacity, thus decreasing sports performance (Beilock et al., 2006). Athletes with lower working memory capacity are more likely to experience decreased accuracy, poor decision-making, or choking under high-pressure conditions (Hardy et al., 1996). Working memory itself may fluctuate due to situational stress, which can affect decision quality and, consequently, performance outcomes. Furley and Memmert found that elite basketball players are better able to concentrate on decision-making tasks while ignoring distractions, scoring higher on working memory capacity tests (Furley and Memmert, 2010). Another way working memory affects performance is through attentional control (Eysenck, 1998). Compared to players with lower working memory capacity, those with higher levels are better at focusing attention and making sound decisions in everyday life (Broadbent et al., 1982).

Furleyand and colleagues found through their research on ice hockey players that working memory capacity can predict the degree to which players adjust their decision-making behavior based on real-life scenarios. Research has shown that ice hockey players with high working memory capacity are able to autonomously adjust inappropriate attack plans and usually do not blindly follow predetermined tactical guidance (Furley and Memmert, 2012). Bisagno et al. found through regression research that working memory can serve as a predictor of volleyball performance, with higher levels of working memory indicating better volleyball performance (Bisagno and Morra, 2018). Wood et al.'s research suggests that individuals with smaller working memory capacity are more likely to experience anxiety and attentional impairment in stressful environments, thereby affecting athlete performance on the field (Wood et al., 2016). The results of this study indicate that working memory capacity can not only predict an individual's ability to control attention well but also predict athletes who may fail under high stress. The impact of working memory on sports performance is also reflected in the training stage. Coaches often provide specific instructions during practice or competition, and guide athletes to enter a prepared state of exercise, thereby helping athletes reduce the complexity of decision-making. This approach improves athlete performance by directing their attention in a targeted manner.

Compared to projects with higher levels of automation, tactical decision-making sports rely more on working memory. Mayers et al. found through cross-sectional research that there is a positive correlation between working memory and the performance of football players, and a higher level of working memory can enhance the performance of football players (Mayers et al., 2011). Some scholars have also found in their research that after cognitive-motor dual-task training (including working memory), basketball control performance is better than the group without cognitive-motor dual-task training because cognitive training stimulates the cognitive function necessary for fast and accurate basketball dribbling (Bisagno and Morra, 2018). But it is also related to the state of cognitive load. When the cognitive load is low, individuals have a greater ability to mobilize and control cognitive resources, improve working memory efficiency, and create possibilities for athletes to perform exceptionally well (Botvinick et al., 2001). On the contrary, it will weaken the efficiency of working memory and lead to abnormal motor performance (Baumeister, 1984). Therefore, enhancing working memory ability with tACS is beneficial for improving sports performance.

4.2 Impact of learning ability on sports performance

Learning ability is an important component of cognitive ability and the main way of acquiring motor skills. Learning

TABLE 4 The effect of different frequencies of transcranial alternating current stimulation on cognitive function.

Frequency band	References	Frequency (Hz)	Cognitive tasks	Cognitive function	Intervention effect
θ(4–7)	Wolinski et al. (2018)	4	Retrospective working memory	Working memory	Improve the working memory of the subjects
	Wischnewski et al. (2016)	5	A modified version of the sequential gambling task	Decision-making ability	Improved perception of uncertainty
	Violante et al. (2017)	6	Visual-spatial working memory task	Working memory	Improved working memory performance
	Wischnewski et al. (2016)	6	Reverse learning tasks	Learning ability	Reverse learning speeds up
	Dantas et al. (2021)	6.5	Cambridge Gambling Mission	Decision-making ability	Reduced motivation for risk decision-making behavior
α(8–13)	Borghini et al. (2018)	10	Retrospective working memory	Working memory	Improving the working memory of participants
β(14–30)	Yaple et al. (2017)	20	Risk decision-making for voluntary task-switching	Decision-making ability	Increased motivation for making risk decisions
	Zhang et al. (2022)	20	SRTT	Learning ability	Shortened reaction time
	Pollok et al. (2015)	20	SRTT	Learning ability	Can improve motor skills and sequence response skills
	Minpeng et al. (2019)	25	SRTT	Learning ability	Reduced learning response time for motion sequences
γ(30–80)	Pollok et al. (2015)	35	SRTT	Learning ability	The promotion effect on learning motion sequences is not significant
	Borghini et al. (2018)	40	Change detection task	Working memory	Improved working memory ability
	Zhang et al. (2022)	70	SRTT	Learning ability	Improved learning ability
	Miyaguchi et al. (2018)	70	Visual motion control	Learning ability	Significant reduction in task error rate

ability helps to consolidate motor memory, reduce the attention required during exercise, make the movement more automated, improve the economy of movement, and in sports, it manifests as quickly acquiring motor skills and shortening the adaptation cycle (Fresnoza et al., 2020).

Nitsche et al. (2003) argue that the acquisition and early consolidation stages of motor skills require the involvement of motor learning. Using tDCS to stimulate the M1 brain area can significantly improve the performance level of motor learning, and promote the acquisition and maintenance of motor skills. Hillman et al.'s research also supports this point, believing that learning ability plays a role in skill acquisition. Higher learning ability can encourage athletes to be better at acquiring sports skills through observation, imitation, and analysis, and can quickly reach the autonomous stage of mastering sports skills, reduce cognitive load during exercise, and thus improve sports performance (Hillman et al., 2008). Kidgell et al. (2013) demonstrated through experiments that stimulating the M1 region with tACS (unilateral and bilateral) can improve learning ability. When completing Purdue pegboard test, motor performance significantly improves, with sustained effects reaching up to 60 min. Scholars such as Zhu used cathode tDCS to stimulate the left DLPFC, which also improved performance in sports learning and golf putting practice (Zhu et al., 2015). The reason may be that the enhancement of learning ability helps cultivate athletes' ability to correct sports movements, reduce errors in sports events, and improve the accuracy and economy of movements (McCullagh and Weiss, 2001). Faubert (2013) believe that athletes with fast learning abilities in unpredictable and complex dynamic scenes have better competitive performance. Moreover, in the study, it was found that professional athletes with stronger learning abilities completed better tracking tasks when completing multi-objective tracking tasks. On the other hand, some scholars believe that improving learning ability can help athletes better manage emotions and stress, improve self-efficacy, increase their confidence in completing actions, effectively reduce negative emotional interference, and ultimately improve sports performance (Starek and McCullagh, 1999). The above studies all indicate that the enhancement of learning ability is beneficial for athletes to quickly master sports skills and reduce movement errors in sports, which has a positive effect on improving sports performance.

There is a correlation between working memory and new skill learning. Recent research has begun to explore the role of working memory in motor learning, finding that working memory capacity can predict the learning outcomes of categorization tasks and the ability to solve mathematical problems (Beilock and Carr, 2005).

Working memory plays a role in both visuomotor adaptation and motor sequence learning, particularly in the early stages of learning. Greater working memory capacity leads to stronger learning abilities, which in turn significantly enhance sports performance (Anguera et al., 2010). Therefore, tACS that boosts learning ability can improve sports performance.

4.3 Impact of decision-making ability on sports performance

Decision-making is a cognitive process of making choices between two or more options. Sports decision-making is an advanced stage of cognitive processing for athletes, which is a more comprehensive ability compared to working memory and learning ability. Therefore, decision-making requires the participation of more brain regions, which is very common in sports such as football, basketball, volleyball, etc. that require cooperation from multiple people (Hwang et al., 2022).

Short decision-making time is a characteristic of the sports field, especially in competitive sports. For complex and open sports, the level of sports decision-making directly affects the performance of athletes in terms of technical skills and athletic performance (Fu, 2004). On the sports field, athletes instantly integrate their own and opponent's situational information, perform high-speed and efficient processing, and quickly make judgments. Athletes with higher decision-making abilities can quickly and accurately make judgments and decisions on current tasks, avoiding choking effects and maintaining or even improving sports performance (Wang, 2013). On the contrary, incorrect sports decisions may choose the wrong tactics or techniques, which will directly lead to a decline in sports performance and even affect the score of the game. In high-level competitive events, the outcome of the competition does not depend on the factors of athletic skills, but on the choice of skills and tactics by the athletes. Elite athletes exhibit both accurate and reasonable decision-making performance because they have a reasonable cognitive structure toward sports scenes, and they can effectively allocate attention resources based on their cognitive advantages (Humphreys and Revelle, 1984).

Some scholars believe that the differences in sports performance among elite athletes are caused by differences in information selection and decision-making (Yan and Zheng, 2008). Some scholars even believe that there is a positive correlation between sports performance and sports decision-making. Athletes with higher sports decision-making abilities are faster in cognitive processing, and the higher the speed of sports decision-making, the higher the level of sports; When the decision-making ability of sports decreases, the accuracy of sports decision-making decreases, and the decision-making time becomes longer, which will reduce sports performance. Therefore, the level of sports decision-making ability can to some extent distinguish the level of athlete sports (Gilovich, 1984). In football matches, the level of athletic decision-making determines the upper limit of an athlete's athletic level at the same technical level (Xuanpeng, 2024). Sports decision-making ability enables athletes to make the best choices in evaluating potential risks and benefits, reducing the occurrence of sports errors due to blind decision-making. Huijgen et al. (2015) found in football that good sports decision-making is related to the athlete's accurate evaluation of the ball's trajectory and ability to catch the ball, as well as the athlete's ability to choose the best passing time and place teammates in the best scoring position. It is important for the performance of football players, and when decision-making ability decreases, it can affect the athlete's decision to make accurate shooting targets. The decision-making speed in complex tactics can be enhanced with training, and the decision-making speed is also an indicator of the level of sports skills. Li (2019) found in their research that sports decision-making training can effectively improve the decision-making speed and accuracy of basketball players during the passing process, thereby enhancing their performance on the field. When sleep deprivation leads to a decrease in the speed of sports decision-making, basketball players' performance also decreases. Amann et al. found in their research that exercise decision-making is crucial for endurance performance, as it determines whether to continue with endurance exercise (Amann and Secher, 2010). The above research indicates that sports decision-making not only affects individual sports performance but also affects group exercise performance. Therefore, enhancing exercise decision-making ability is beneficial for improving exercise performance.

The capacity of working memory is closely related to decision-making, and working memory is the guarantee of information processing in the decision-making process (Kane et al., 2007). Athletes with low working memory capacity are more likely to make decision errors in stressful situations, and improving their working memory capacity can improve sports decision-making (Chi et al., 2014). Furley and Memmert observed the relationship between working memory capacity and the anti-interference ability of ice hockey players in complex decision-making tasks by setting up interference scenarios (Furley and Memmert, 2012). The results showed that the high working memory capacity group had a higher probability of correct decision-making than the low working memory capacity group. The reason is that sufficient working memory capacity is the fundamental guarantee for timely updating competition information and making correct decisions in complex sports decision-making scenarios. Therefore, it can be seen that working memory capacity can play a positive role in sports decision-making. However, some research results are different from the above. For example, athletes are prone to the phenomenon of "choking" at critical moments in a competition, which is mainly influenced by the capacity of working memory. Athletes with higher working memory are often more likely to perform poorly in competitions. A possible explanation for this phenomenon is that athletes with higher working memory tend to use the working memory system when solving problems during the competition. Once the stress and anxiety of the competition interfere with the normal operation of the working memory system, it will cause a sudden decline in the athlete's sports decision-making ability, ultimately leading to a decline in sports performance (Chen and Liu, 2009; Wang, 2003). The above studies all indicate that the enhancement of sports decision-making can improve sports performance.

With the increasing recognition and support of coaches and athletes for the idea that "competition requires cognitive ability,"

how to use tACS to enhance cognition has become a common concern for researchers, coaches, and athletes.

5 Development of intervention plans for tACS

In practical applications, it has been found that the intervention effect of tACS on cognition exhibits high variability, among which stimulus frequency, stimulus location, stimulus intensity, stimulus time, and athlete's state are important factors affecting the intervention effect (Klink et al., 2020). However, the intervention plan for tACS has not been standardized yet, and there are differences in intervention plans among different cognitive functions. Therefore, clarifying the constituent elements of the tACS intervention plan and its impact on cognitive function can help develop a refined tACS intervention plan, thereby improving the safety factor and application effect of tACS.

5.1 Stimulation frequency

Unlike other TES, tACS regulates brain oscillations through a unique current frequency, and brain oscillations of different frequencies are closely related to cognitive function. Therefore, the current frequency of tACS can significantly affect cognitive function (Morillon et al., 2019; Table 4).

The cognitive function affected by different stimulation frequencies varies, and there are five commonly used tACS stimulation frequencies, among which delta frequency range is 0–4 Hz; theta frequency range is 4–7 Hz; alpha frequency range is 8–13 Hz; beta frequency range is 13–30 Hz; gamma frequency range is 30–80 Hz (Klink et al., 2020). Research has found that (1) tACS stimulation of the different frequency can affect different cognitive functions, theta frequency stimulation is mainly related to working memory, the position of the parietal lobe theta Oscillation can improve the performance of working memory (Tseng et al., 2018); alpha frequency stimuli are mainly associated with executive function, visual attention, and memory processes (Kim et al., 2017; Taylor and Thut, 2012; Mierau et al., 2017); beta frequency stimulation is related to attention, working memory, and executive control (Engel and Fries, 2010); gamma frequency stimulation is related to the processing of input information, working memory, and situational memory (Fries, 2015; Pina et al., 2018; Nyhus and Curran, 2010). Analyzing the above studies, it was found that most tACS frequencies can affect working memory, possibly due to the wide band of working memory, and multiple frequencies of tACS can cause oscillations in the band of working memory. (2) Further research has found that different frequencies of tACS can also affect the same cognitive function, for example, some scholars have proposed beta stimulation can promote both motor learning and executive function (Schmidt et al., 2019), alpha stimulation can also inhibit executive function; When verifying the impact of α-tACS and θ-tACS on motion decision-making ability, Soutschek found no significant difference between the two (Soutschek et al., 2022). (3) Same frequency band will also have different effects on the same cognitive function. Wolinski found in his research that even if they all belong to the same category theta frequency of the band can also have a different effect on cognitive function. 4 Hz can deepen working memory, while 7 Hz cannot. (4) Stimulating effect of tACS is influenced by individual status. Due to the neural oscillation effect of input, the endogenous state of the subject's brain also greatly affects the intervention effect of tACS (Reato et al., 2013). For example, Axmacher and his colleagues found that as the workload of working memory increases, the theta frequency of the brain decreases, while there is no significant effect on the gamma frequency. When using tACS in the theta frequency band for stimulation, it does not always improve an individual's working memory ability (Axmacher et al., 2010). The θ-γ cross-frequency coupling theory posits that slower theta frequencies integrate more gamma cycles within each theta cycle, thereby increasing memory capacity (Lisman and Idiart, 1995). Conversely, faster theta frequencies incorporate fewer nested gamma cycles, leading to reduced memory capacity. Therefore, understanding individual differences is crucial for optimizing the effectiveness of tACS, which explains the variability in outcomes when the same stimulation is applied by different researchers (Sauseng et al., 2019). Fröhlich (2015) also suggest that tACS influences ongoing brain oscillations by altering their frequency, with the impact largely dependent on the brain's endogenous state and the EEG frequency of different functional regions.

Ali et al. (2013) believe that brain oscillatory activity is a periodic dynamic system that has an optimal response frequency. When the frequency of external stimuli reaches or approaches the resonance frequency of the brain network, the regulatory effect on neurons is strongest. Therefore, many scholars are committed to finding personalized tACS frequencies based on the endogenous oscillation frequency of the subject to increase the regulatory effect on cognitive function. Reinhart et al. confirmed the personalized internal frequency of each elderly subject by pre-collecting and analyzing task state EEG signals and then used this frequency as the stimulation frequency of high-precision tACS to regulate the working memory ability of the elderly. The results showed that the performance of working memory tasks significantly improved after stimulation and had better regulatory effects compared to fixed-frequency stimuli (Reinhart and Nguyen, 2019).

5.2 Phase

Among the factors that affect the effectiveness of tACS interventions, phase is often overlooked, but there is currently limited research on the phase of tACS. Due to the phase energy determining the relative positions of the peaks of endogenous and exogenous oscillations, the intervention effect of tACS is closely related to the endogenous oscillations in the brain, which can greatly affect the effectiveness of tACS.

In phase (phase difference of 0°) tACS stimulation can improve cognitive function, while out of phase (phase difference of 90 and 180°) tACS stimulation can reduce cognitive function. When the current waveform of tACS is sinusoidal AC, its phase can determine the intervention effect of tACS (Ishii et al., 1999). Placing the electrodes of tACS in different brain regions and setting their parameters can regulate the neural oscillatory activity between two brain regions, thereby altering information exchange

TABLE 5 The effect of transcranial alternating current stimulation on cognitive function in different brain regions.

References	Brain region Effect of action	Electrode position	Cognitive function	Intervention effect
Zhang et al. (2022)	Left motor cortex	Left M1 and above the right eye socket	Sports learning	Shortened reaction time
Nguyen et al. (2018)	Frontal cortex	MFC and Right LPFC	Learning ability	Improve learning ability
Sela et al. (2012)	Frontal cortex	DLPFC, F3	Sports decision-making	Reduce motivation for sports decision-making
Yaple et al. (2017)	Left frontal lobe	F3, Ipsilateral deltoid muscle	Sports decision-making	Increase motivation for sports decision-making
Yaple et al. (2017)	Right frontal lobe	F4, Ipsilateral deltoid muscle	Sports decision-making	Reduce motivation for sports decision-making
Wischnewski et al. (2016)	Prefrontal cortex	AF3 and AF4 outer 2cm, Fc1 and Fc2 outer 1cm	Sports decision-making	Increase the ability to perceive uncertainty
Jaušovec and Jaušovec (2014)	Left frontal lobe	F3; Right supraorbital forehead	Working memory	Improve working memory performance
Violante et al. (2017)	Frontal, parietal, and temporal lobes	(F4/P4), T8	Working memory	Improving speech working memory performance
	Left frontal and parietal lobes	DLPFC(F3), (CP5)	Sports decision-making	Reduce motivation for sports decision-making
Borghini et al. (2018)	Parietal cortex	P3, P4	Working memory	Improve working memory performance
Tseng et al. (2018)	Parietal cortex	(P3/P4), Left cheek	Visual working memory	Improve working memory performance
Bender et al. (2019)	Parietal cortex	(P4)+(Cz)	Working memory	Improve working memory performance

between brain regions (Zaehle et al., 2010). For tACS stimulation in both brain regions, different phases of alternating current will produce different effects. Polanía et al. (2012) applied in-phase tACS (phase difference 0°), out-of-phase tACS (phase difference 180°), and false stimuli to the frontal and parietal regions of the subjects to investigate the effects of different phase tACS stimuli on executive function. The results showed that compared to false stimuli, in-phase stimuli significantly increased the response time of participants in task execution, while antiphase stimuli reduced task performance. This indicates that changes in the phase of tACS can affect the level of cognitive task completion. The study by Polania et al. also confirms this point, that in-phase theta frequency band tACS can reduce the reaction time in visual memory matching tasks, while the opposite reduces performance and increases reaction time (Polanía et al., 2012).

The synchronous phase stimulation of the frontal and parietal lobes can promote the improvement of working memory ability (Violante et al., 2017). Polania R's research found that the left prefrontal cortex and parietal cortex are in the same phase theta Stimulation can improve visual working memory, while the opposite is true theta Stimulation can reduce the performance of working memory (Polanía et al., 2012). Violante et al. further investigated the neural mechanisms underlying the impact of in-phase tACS on verbal working memory when stimulating the frontal and parietal lobes (Violante et al., 2017). The results indicate that the same phase frontal lobe θ-tACS stimulation can enhance the behavioral performance of working memory; The fMRI results showed that the same phase tACS stimulation in the frontal and parietal lobes can regulate brain activity and functional connectivity, and it was found that this regulatory effect is related to phase and the cognitive state of the subjects. That is, when the subjects perform high cognitive load tasks, the same phase tACS enhances the activation and functional connectivity of the frontal and parietal lobe brain regions, enhancing cognitive function. Some scholars also believe that the intervention effects of different tACS phases are related to the cognitive level of the subjects. Tseng found in his study of the impact of tACS on visual working memory that the same phase θ-tACS induces improvement in visual working memory performance, but only in low-level individuals, while high-level individuals may experience mild visual working memory damage. In another experiment, the reverse phase θ-tACS is not helpful for low-level individuals, but significantly impairs the visual working memory capacity of high-level individuals (Tseng et al., 2018). The reason may be that when cognitive function is at a high level, it often exhibits more complex neural signals. When using reverse tACS stimulation, may damage the phase relationship between endogenous and exogenous factors in high-performance individuals, reducing the brain's ability to process information (Costa et al., 2002).

Tseng et al. (2018) believe that the phase of brain oscillations reflects the encoding and retrieval status of the brain network, and the relative phase of oscillations increases the success rate

of encoding and retrieval in the memory process. Therefore, when using the same phase Tacs to stimulate the frontal and parietal lobes, can improve the subject's working memory ability. Similarly, Sauseng et al.'s study found that when participants performed visual-spatial working memory tasks, there was a difference between the frontal and parietal lobes theta frequency band exhibits phase synchronization characteristics, indicating that phase synchronization within the Fronto Parietal Network (FPN) can improve the maintenance time of information in the working memory process (Tseng et al., 2018). Daume also found phase synchronization between the frontal and temporal lobes when studying them. Daume et al. (2017) used Magneto encephalo graphy to investigate brain activity during the retention phase of a delayed-match task. The results revealed phase synchronization between the left inferior temporal cortex and the prefrontal cortex in the lower frequency bands (θ/α bands) during the retention period. Additionally, they observed increased phase-amplitude coupling between the phases of theta and alpha bands and the amplitude of the beta band in the left inferior temporal cortex.

Phase differences are not solely related to exogenous frequencies but are also influenced by the endogenous frequencies of individual brain regions. When exogenous and endogenous frequencies align, the likelihood of phase synchronization increases. Reinhart et al. analyzed task-state EEG signals to determine each older participant's individualized internal frequency. This frequency was then used as the stimulation frequency for high-definition transcranial alternating current stimulation (HD-tACS) to modulate working memory performance in older adults. The results indicated that personalized HD-tACS could restore theta band phase synchronization between the frontal and temporal lobes during the retention period. Additionally, there was a significant increase in θ-γ phase-amplitude coupling (PAC) in the temporal region, leading to improved performance on working memory tasks (Reinhart and Nguyen, 2019).

In summary, in-phase tACS stimulation is beneficial for enhancing cognitive function, while anti-phase tACS stimulation can decrease cognitive function. When in-phase tACS is applied to the frontal and parietal lobes, the intervention has a greater impact on executive function and working memory. The effectiveness of in-phase tACS intervention is also related to the individual's cognitive level; the lower the cognitive level, the better the in-phase tACS intervention works.

5.3 Brain stimulation areas

The brain stimulation area is the area directly in contact with tACS stimulation. The cognitive functions represented by different brain regions in the brain are both overlapping and different. This study found that different brain regions have their advantages in cognitive functions. Therefore, exploring the stimulation of tACS in different brain regions is of great significance for targeted improvement of cognitive function. At present, in the intervention plan of tACS, the main brain regions stimulated are the frontal and parietal lobes. When stimulating the frontal lobe, the effects are diverse and can improve cognitive functions such as motor decision-making, working memory, motor learning, and attention; when stimulating the parietal lobe, the effect is relatively single, mainly having a positive effect on working memory (Table 5).

Research has found that both the frontal and parietal lobes have a positive effect on working memory, with the parietal lobe playing a central role in working memory. Jaušove et al. found that tACS stimulation on the left (P3) or right parietal lobe (P4) had a positive effect on working memory, but no such positive effect was observed on left frontal lobe (F3) stimulation (Jaušovec et al., 2014). Violante also proved this point, finding that in demanding working memory tasks, the right frontal-parietal network associated with task activation has a direct connection with brain synchronization (Violante et al., 2017). Further research has found a high correlation between the right frontal-parietal brain area and memory function, and the parietal lobe plays a central role in influencing memory function (Curtis and D'Esposito, 2004). Vossen applied 6 Hz tACS stimulation to the left frontal lobe (F3) and left parietal lobe (P3) cortex, respectively, and found that only when tACS was applied to the left parietal cortex did the visual working memory storage capacity improve. This supports the central role of the parietal lobe brain region in working memory storage capacity, and this finding has been confirmed in multiple neuroimaging studies (Vossen et al., 2015; Champod and Petrides, 2010). The impact of tACS electrode stimulation on cognitive function varies in different regions of the brain. Stimulating the frontal and parietal regions at F3-P3 may regulate the frontal striatal network related to motor decision-making, or the frontal parietal network related to voluntary executive control (Rao et al., 2008). When stimulated in F3-F4, it can modulate the frontal and deep medial structures (Bai et al., 2014), while the F3-P3 electrode may modulate the frontal and parietal structures, indicating that stimulating the left frontal lobe or inhibiting the right frontal lobe increases decision-making ability (Orr and Banich, 2014). Stimulation of both the frontal and parietal lobes can enhance working memory ability, but the parietal lobe is the core area that enhances working memory. Parietal lobe θ-tACS stimulation improves the accuracy of working memory, while frontal lobe stimulation θ-tACS stimulation shortens the working memory response time, indicating that even if the same cognitive function is affected by different brain regions, there are differences in the changes in cognitive function.

Numerous studies by scholars have shown that the frontal lobe is related to motor decision-making and plays an important role in voluntary risk decision-making. For example, Rao et al. (2008) demonstrated a link between the prefrontal cortex and voluntary acceptance of greater risk, suggesting that the prefrontal cortex regulates the active willpower control of risk-takers by controlling executive components. The ventral striatum is located behind the frontal lobe, and activation in this area indicates the making of risk decisions. As decision rewards increase, the probability of activation also increases. Therefore, stimulating the frontal lobe may enhance decision motivation because tACS stimulation affects the deep ventral striatum position (Rao et al., 2008; Niv et al., 2012). Moreover, due to the asymmetry of the brain, even when

TABLE 6 Common different stimulation doses of tACS.

References	Cognitive function	Current intensity (mA)	Stimulation duration (min)	Electrode size (cm^2)
Jaušovec and Jaušovec (2014)	Working memory	1–2.25 (pp)	15	All 5 * 5
Tseng et al. (2018)	Working memory	1.6 (pp)	20–24	(4*4), (5*7)
Violante et al. (2017)	Working memory	1 (pp)	20	All 5 × 5
Bender et al. (2019)	Working memory	2 (pp)	Synchronize with tasks (60 task experiments)	19.6, 4.9
Borghini et al. (2018)	Working memory	1.5 (pp)	20	All 5 × 7
Wolinski et al. (2018)	Working memory	1.24 ± 0.3 mA	12	All 5 × 5
Pollok et al. (2015)	Sports learning	1 (pp)	12 min 12 s	All 5 × 7
Zhang et al. (2022)	Sports learning	1 (pp)	11	All 5 × 7
Minpeng et al. (2019)	Sports decision-making	0.5 (pp)	15	All 5 × 5
Wischnewski et al. (2016)	Sports decision-making	0.5 (pp)	30	All 3 × 5

electrical stimulation is performed in different brain regions of the same lobe, the stimulation effect varies. Sela et al. θ-tACS is applied to the left or right dorsolateral prefrontal cortex, and participants perform decision-making tasks that require risk-taking. Sela used tACS with a frequency of 6.5 Hz and an intensity of 1 mA to provide stimulation for 15 min during the task. A group of subjects received tACS stimulation in the left prefrontal cortex, while a group of subjects received tACS stimulation in the right prefrontal cortex. The results showed that only the stimulation in the left hemisphere had a significant impact on motor decision-making. Compared with the stimulation in the right hemisphere and false stimuli, participants with left stimulation had higher motor decision-making motivation (Sela et al., 2012). This discovery has also been confirmed by other scholars. When Dantas stimulated the left frontal lobe in the experiment, the motivation for adventurous motor decision-making decreased; when stimulating the right frontal lobe, the motivation for adventurous exercise decision-making increased. This may indicate a potential functional correlation between asymmetry in the left and right frontal lobes and risky decision-making (Dantas et al., 2021; Badre et al., 2012).

Some scholars also believe that the relationship between stimulating brain regions and cognitive function cannot be clearly defined. The reason may be that the maximum value of tACS stimulation is not located at the stimulation site. Bikson et al. modeled the current in the brain and found that when stimulating the primary motor cortex, the maximum current value does not lie below the electrode, but spreads to the frontal cortex (Bikson et al., 2010); Moreover, the brain is a complex network structure, and there is currently a lack of clear understanding on whether the stimulation of a specific brain area alone causes changes in the activity of other brain areas, thereby enhancing cognitive function. Therefore, it cannot be determined whether the change in cognitive function is a unique effect of tACS stimulation on a specific brain area, or whether similar effects can be observed by stimulating other cortical areas. Scholar Okada believes that the stimulation of brain regions by tACS is not a simple change in the stimulated area, but rather a strengthening of the connections between different brain regions. However, most experiments have not monitored changes in oscillatory activity or excitability during the stimulation process, and there is a lack of direct evidence to prove that excitability changes in the target area affect cognitive function. Therefore, clarifying the relationship between stimulated brain regions and cognitive function is still under exploration (Okada et al., 2004).

In summary, the reason why the frontal and parietal lobes are ideal targets for tACS stimulation may lie in two aspects: (1) because their anatomical location is relatively shallow and easy to approach; (2) Neuroimaging studies have shown that the frontal lobe can affect a wide range of cognitive functions, including working memory, attention, learning, creative thinking, and social functioning. Therefore, most current studies support the frontal lobe as the main stimulus area affecting cognitive function (Duncan and Owen, 2000).

5.4 Stimulation dose

The size of the stimulation dose is related to the stimulation intensity, stimulation time, and electrode size, and is an important factor affecting the stimulation effect. A single stimulation plan not only cannot improve the application effect of tACS but may even cause irritating injury to the subjects (Peterchev et al., 2012). Based on previous research, most current studies have found that the stimulation parameters are as follows: the peak current intensity is between 0.5 and 2 mA, the stimulation time is between 6 and 40 min, and the electrode size is between 9 and 35 cm^2. The most commonly used parameters are: the peak current is 1 mA, the stimulation time is 20 min, and the electrode size is 35 cm^2.

With the deepening of research, scholars have found that different stimulation doses may have different effects on cognitive function. More accurate stimulation doses are conducive to the application effect of tACS in cognitive function. Currently, current intensities with peak values of 0.5–2 mA are commonly used in clinical practice (Table 6). The current intensity in this area can not only have a good intervention effect but also avoid skin burns

caused by excessive stimulation intensity. The changes in cortical excitation depend on changes in tACS intensity. For example, a low stimulation intensity of 0.4 mA can lead to an increase in cortical excitation threshold, which in turn reduces excitability (Moliadze et al., 2012); Scholar Vöröslakos believes that a high current should be used. Low current intensity cannot overcome the consumption of scalp/skull shunting, and residual current cannot affect cortical excitation. Therefore, a higher current intensity may be needed to fully overcome skin/skull shunting, and it is recommended that the stimulation intensity of the current be above 2 mA (Vöröslakos et al., 2018). Moreover, when the stimulation is sufficiently strong, new neural oscillations can be triggered by the current intensity, making the intervention more effective. However, excessive current can also stimulate the skin and cause damage, so increasing the current intensity to enhance the effect while ensuring safety is a future research direction (Liu et al., 2018). Stimulation time is also an important factor affecting intervention effectiveness (Stagg et al., 2018). The intervention time of tACS is usually divided into two types: one is synchronous with cognitive task time, and the other is a fixed time, usually 20 or 30 min, with a single time usually not exceeding 40 min. The reason is that long-term stimulation of tACS can disrupt the stable state of synapses, leading to a decrease in intervention effectiveness (Batsikadze et al., 2013).

At present, there are no strict regulations on the size of electrodes. However, research suggests that under the premise of a certain current, the size of the electrode will affect the current density, and current density is a key factor affecting individual tolerance. Moreover, current density is also influenced by current intensity, and there is currently a lack of research on current density. Therefore, most studies on stimulus dose focus on stimulus intensity and duration. At present, some studies suggest that traditional large electrodes (5 *7 cm^2) can cause current dissipation and affect other brain regions, making it difficult to confirm the detailed relationship between regulatory effects and cognitive function. Therefore, to clarify this relationship of changes, more small-area stimulation electrodes are used. Dmochowski found in his research that when multiple small electrodes are used, the stimulation target of tACS is more focused, and the stimulation effect can be significantly enhanced (Dmochowski et al., 2011). Therefore, many scholars have also called for the use of small electrodes with multiple stimulation sites for tACS electrodes. However, currently, most studies still use large-area stimulation electrodes, possibly because the mechanism of action of tACS is to induce endogenous oscillations in the brain through alternating current, rather than relying on stable electric fields to stimulate the brain. However, currently most studies still use large-area stimulation electrodes, possibly because the effectiveness of tACS is related to the frequency of tACS and independent of electrode size. The second reason may be that large-area electrodes are more convenient to operate than small-area electrodes.

In summary, tACS stimulation should have different doses for specific cognitive functions. The basic principle is to first select the target area for stimulation based on the regulated cognitive function, then select the size of the electrode and determine the intensity of the stimulation to avoid electrical stimulation injury; finally, select the stimulation time based on the cognitive task (Table 6).

5.5 Other factors affecting the effectiveness of tACS intervention

Based on formulating intervention plans for tACS, the brain state, timing of application, and target audience will also affect the intervention effect of tACS. Research has found that: (1) the intervention effect of tACS is related to individual cognitive needs, and the higher the cognitive needs, the better the effect of tACS intervention on improving cognitive function (Violante et al., 2017). The reason may be that when an individual's cognitive function is worse, there is a greater demand for cognition, making it difficult to achieve the "ceiling" effect. Therefore, tACS has a greater effect on improving cognitive function (Kardos et al., 2014; Moliadze et al., 2019). (2) The effect of tACS on cognitive function is also influenced by eye state. Nguyen J et al. found that 6 Hz tACS enhances learning ability when subjects are in an eyes-open state. However, when subjects are in an eyes-closed state, the enhancement in learning ability is not significant. This may be due to the eyes-open state enhancing executive processes, promoting neuroplastic changes in theta functional connectivity between the MFC and lPFC, thus improving learning ability (Nguyen et al., 2018). (3) The application timing of tACS can be divided into before the task, during the task, and after the task; in practical applications, it is mostly before and during the task. (4) The application of tACS in different populations also has differences in effectiveness. The effect of tACS on patients with cognitive impairment is higher than that on healthy individuals, and its effect is more significant in the elderly population (Qi et al., 2023).

6 Ethical risks of using transcranial alternating current

"Putting people first" is the origin of competitive sports and the foundation for the healthy development of competitive sports. Therefore, for ethical considerations, it is crucial to explore whether the use of tACS will violate the regulations of the World Anti-Doping Agency (WADA) regarding its use. According to the requirements of the WADA code (The World Anti-Doping Agency, 2020), if a substance or method meets any two of the three standards, it will be considered for inclusion in the International Standard Prohibited List of the WADA (hereinafter referred to as the Prohibited List). According to the "Prohibited List," prohibited substances and methods are classified as prohibited within the competition, prohibited on all occasions, and prohibited for special projects (Imperatori et al., 2018). Current research indicates that tACS can improve athletic performance by enhancing cognitive abilities, and no actual or potential harm to the health of athletes has been found when using tACS. Therefore, whether tACS will be banned by the World Anti-Doping Agency largely depends on whether its use violates the spirit of sports.

After research, it was found that tACS may be inconsistent with the advocated sportsmanship in the following three aspects.

- May have increased inequality. tACS, which can improve cognitive function, may also increase competitive inequality among athletes. Due to the different costs of obtaining

tACS, athletes from different countries and regions may have differences in their use of tACS. This may result in some athletes being able to easily use tACS while others are unable to use it, leading to athletes who can use tACS devices gaining an advantage in competition. The application of tACS may also result in training inequality. Some scholars have found in their research that tACS can enhance cognitive function, while others have not found that tACS cannot enhance cognitive function (Pollok et al., 2015; Wischnewski et al., 2016). Therefore, the effect of tACS on exercise performance has both positive and negative aspects. The reasons for this include the intervention plan of tACS, the state of athletes, etc. Therefore, the statement that tACS improves exercise performance is not entirely consistent, which is not a problem in scientific research, but it is very important in the recognition of the World Anti-Doping Regulations. If athletes can improve their athletic performance without working hard during training, it will increase the inequality among athletes during training.

- There is a risk of policy loopholes. At present, there is no known method that can reliably detect whether an individual has recently undergone optimization with tACS stimulation, making neural stimulants almost undetectable, making it impossible to confirm whether an individual has used tACS to improve cognitive function before the competition (Park, 2017). When tACS emerged as a new technology, there was an imbalance between existing anti-doping policies and emerging technologies, and existing policies could not explain well whether tACS had violated the World Anti Excitement Regulations (Rodenberg and Hampton, 2013). For example, due to the lack of advanced testing methods to identify athletes who may abuse this technology, genetic stimulants were not included in their banned technology list until 2009 (Fore, 2010). However, some scholars have used monitoring BDNF to determine whether individuals have used tDCS intervention, which provides direction for monitoring the use of tACS. However, further empirical evidence is still lacking (Donati et al., 2021). Perhaps there will be methods for detecting nerve stimulants in the future, but they should be as cheap and easy to obtain as possible to ensure the people-oriented spirit of sports.
- Clarify what sports spirit is. There is no clear standard for evaluating sportsmanship in the World Anti-Doping Regulations, and there may be differences in the understanding of sportsmanship between athletes and the World Anti-Doping Agency. How to use tACS without violating the sportsmanship spirit of the World Anti-Doping Regulations? Imperatori once stated in his discussion of the application of tDCS that even small changes to tDCS can have a significant impact on sports outcomes for elite athletes. Therefore, it is recommended to only use tACS in training, while it should be prohibited in competitions. tACS is similar to tDCS and seems to be subject to similar constraints (Imperatori et al., 2018). However, there is indeed a lack of clear guidelines for the use of tACS (Pugh and Pugh, 2021). At present, scholar Qi and colleagues pointed out in their research that since tACS does not cause actual or potential harm to the health of athletes, nor does it violate the spirit of sport, it does not violate the two-thirds rule of the World Anti-Doping Regulations and is not currently classified as a stimulant (Pugh and Pugh, 2021). However, the spirit of sports is a moral standard related to the value and significance of sports, and there is no consensus on how to evaluate it (Loland and McNamee, 2019).

In summary, tACS does not violate the World Anti-Doping Code in current regulations. However, due to the complexity of tACS intervention programs and the significance of improving exercise performance, the World Anti-Doping Agency may not completely ban the use of tACS in the future but will take certain measures to limit its use, such as allowing the use of tACS to assist training only during the exercise training phase. Therefore, the World Anti-Doping Agency should organize scholars to research the use of tACS as soon as possible, develop a scientifically comprehensive tACS guidance manual, regulate the use of tACS, and minimize the damage to sportsmanship caused by the use of tACS.

7 Reflection and outlook

At present, there is a lack of research on the intervention effects of combining tACS with other treatment methods, and most studies focus on analyzing the individual intervention effects of tACS. There is also a lack of tracking reports on the effectiveness of tACS interventions, and monitoring the effectiveness of tACS interventions is often limited to the same day. Therefore, more research is needed to understand how the subsequent effects of tACS stimulation change over a longer period, to provide more accurate guidance for the application of tACS. In the past, the subjects were mostly healthy individuals or college students, lacking attention to professional athlete groups. The research results under experimental conditions lacked ecological validity. Therefore, more professional athletes should be selected as subjects, and tACS should be applied in actual competitive sports to explore the impact of tACS on athletes' cognitive function, and through what pathways it affects sports performance, thus enriching the application scenarios of tACS and provide technological assistance for athletes to achieve excellent competitive results.

At present, most studies examine the effects of tACS from a behavioral perspective, without evaluating the effects of tACS from the perspective of motor cortical excitability. Therefore, it is difficult to further explain the relationship between behavioral manifestations and the impact of tACS on the neocortex. Moreover, the level at which tACS works is not yet clear. To elucidate the causal relationship between cognitive function and tACS oscillatory activity, it is necessary to apply motor behavior, electrophysiology, and electroencephalography techniques to result in interpretation (Elyamany et al., 2021).

8 Conclusion

tACS intervention is an important means of improving cognitive function, which can enhance the working memory, learning ability, and decision-making ability of athletes and healthy individuals, and has a positive effect on improving sports performance.

The factors that determine the effectiveness of tACS intervention include stimulation frequency, stimulation phase, stimulation area, stimulation dose, etc. The stimulation area and frequency determine which cognitive function tACS affects, whereas the stimulation phase and dose determine the magnitude of the intervention effect. Moreover, before applying tACS, individual cognitive status, age level, and timing of application should be included as factors that affect the effectiveness of tACS intervention, to develop more scientific intervention plans.

Although there is no evidence to suggest significant safety issues with the use of tACS, there are still potential safety risks associated with the promotion and use of tACS among athletes. At present, there is no authoritative organization in China that provides clear operational guidelines for the application of tACS, and there is a lack of safe range values for tACS stimulation parameters. When used in the field of competitive sports, whether it will be recognized as a "nerve stimulant" or have its competition results canceled, authoritative institutions must clarify the usage scenarios of tACS and develop testing equipment for tACS to ensure that the use of tACS intervention can be known.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Author contributions

QW: Writing – original draft, Writing – review & editing. CW: Conceptualization, Data curation, Writing – review & editing. JL: Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Neuromodulation on the ground and in the clouds: a mini review of transcranial direct current stimulation for altering performance in interactive driving and flight simulators

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Transcranial direct current stimulation (tDCS) has emerged as a promising tool for cognitive enhancement, especially within simulated virtual environments that provide realistic yet controlled methods for studying human behavior. This mini review synthesizes current research on the application of tDCS to improve performance in interactive driving and flight simulators. The existing literature indicates that tDCS can enhance acute performance for specific tasks, such as maintaining a safe distance from another car or executing a successful plane landing. However, the effects of tDCS may be context-dependent, indicating a need for a broader range of simulated scenarios. Various factors, including participant expertise, task difficulty, and the targeted brain region, can also influence tDCS outcomes. To further strengthen the rigor of this research area, it is essential to address and minimize different forms of research bias to achieve true generalizability. This comprehensive analysis aims to bridge the gap between theoretical understanding and practical application of neurotechnology to study the relationship between the brain and behavior, ultimately providing insights into the effectiveness of tDCS in transportation settings.

KEYWORDS

transcranial direct current stimulation, tDCS, driving simulator, flight simulator, transportation

1 Introduction

There is robust interest in using non-invasive brain stimulation (NIBS) to characterize and modulate human cognition and behavior (Antal et al., 2022; Berryhill, 2014; Bikson et al., 2018; Dubljević et al., 2014; Wexler, 2017, 2022). NIBS methods have potential applications in demanding scenarios that require cognitive, perceptual, and motor skills, such as driving a car or piloting an aircraft. Both drivers and pilots often encounter challenging situations, like making quick decisions at busy intersections or landing in adverse weather conditions. Performance can also suffer in monotonous situations, such as during partially automated driving (McWilliams and Ward, 2021).

Transcranial direct current stimulation (tDCS) is a prominent NIBS technique that delivers weak electrical currents via scalp electrodes to initiate subthreshold membrane polarization and alter neuronal activity (Nitsche et al., 2008; Nitsche and Paulus, 2000, 2001). The electrical current flows into the brain through the anode, which likely increases cortical

excitability through depolarization, and exits through the cathode, reducing excitability via hyperpolarization (Liu et al., 2018). If a specific brain region is involved in a task, modulating neuronal excitability could enhance or inhibit performance on that task (Knotkova et al., 2019). Typical current intensities range from 1 to 2.5 mA, although currents as high as 4 mA may be used (Chhatbar et al., 2017; Khadka et al., 2020; Reckow et al., 2018). Stimulation should be applied for no more than 1 h during a task (online) or before it (offline) (Woods et al., 2016). While online stimulation may be ideal for immediate performance enhancement, the effects of offline tDCS can last after the stimulation ends and may be better suited for investigating longer-term neural changes (Bikson and Rahman, 2013; Martin et al., 2014; Miniussi et al., 2013; Ohn et al., 2008; Stagg and Nitsche, 2011).

Electrodes are positioned according to standardized electroencephalography (EEG) system coordinates. In conventional tDCS, two large sponge electrodes deliver a broad current across various brain regions (Kuo et al., 2013). High-definition tDCS (HD-tDCS) is a significant advancement utilizing smaller electrodes arranged closely together to achieve more focal current flow than conventional tDCS (Alam et al., 2016; Datta et al., 2009; Villamar et al., 2013). Commonly targeted brain regions include the dorsolateral prefrontal cortex (DLPFC) and the primary motor cortex (Dedoncker et al., 2016; Jacobson et al., 2012). The DLPFC is linked to working memory, cognitive control, and decision-making (Barbey et al., 2013; Krawczyk, 2002; MacDonald et al., 2000), while the primary motor cortex is associated with skill acquisition and procedural learning (Karni et al., 1998). Evidence from functional near-infrared spectroscopy (fNIRS) and event-based magnetoencephalography (MEG) indicates an interaction between the prefrontal cortex and primary motor cortex during critical driving maneuvers, such as accelerating and braking, particularly under varying demands (Foy and Chapman, 2018; Geissler et al., 2021; Walshe et al., 2022).

Importantly, tDCS is generally well-tolerated in both healthy individuals and clinical populations (Antal et al., 2017; Aparício et al., 2016; Bikson et al., 2016; Palm et al., 2018). Compared to other NIBS methods like transcranial magnetic stimulation (TMS), tDCS is portable and adaptable for various settings, from remotely supervised clinical trials (Pilloni et al., 2022) to physically demanding activities like sprint cycling (Garner et al., 2021; Huang et al., 2019) and military operations (Brunyé et al., 2020; Nelson and Tepe, 2015). The cognitive and perceptual enhancement effects of tDCS on operator performance and workload have been examined using computer-based tasks like the Multi-Attribute Task Battery (MATB) (Nelson et al., 2016, 2019; Rao et al., 2024), which was developed by the National Aeronautics and Space Administration (NASA) to mirror the complex responsibilities that pilots manage in flight (Santiago-Espada et al., 2011). Other gamified tasks, like NeuroRacer (Hsu et al., 2015) and Space Fortress (Scheldrup et al., 2014), have also been used for testing.

Investigating tDCS in more immersive environments could further clarify its practical applications. Interactive driving (Fisher et al., 2011) and flight (Allerton, 2009; Hays et al., 1992) simulators offer safe, controlled settings that mimic real-life demands (Roberts A. P. J. et al., 2020). Interactive simulators are effective in predicting on-road driving skills (Walshe et al., 2022) and supporting pilot training (Ross and Gilbey, 2023). With ongoing research supporting its effectiveness, tDCS holds promise for widespread use in cognitive and motor task enhancement. Given the consistent interest in tDCS across clinical, empirical, and commercial contexts, its potential applications for performance enhancement in transportation settings are highly relevant and merit investigation.

2 Current mini review

This review summarizes and evaluates research on the use of tDCS to modulate driver and pilot performance. We conducted searches for refereed articles on Google Scholar and PubMed using the keywords: "driving" OR "flight" AND "transcranial direct current stimulation (tDCS)." This search yielded nine potentially relevant publications. Our scope included studies that recruited healthy participants from nonclinical samples and used interactive driving or flight simulators. Three studies were excluded from review because they did not meet these criteria (Brunnauer et al., 2018; Burkhardt et al., 2023; Pope et al., 2018). Ultimately, six publications met the criteria for inclusion and were reviewed (see Tables 1, 2).

2.1 tDCS and driving simulators

In the earliest study, Beeli et al. (2008) examined the effects of tDCS over the DLPFC on driving metrics such as speed, headway distance, and lane positioning. Currently, outcomes measured in driving simulators lack gold standard metrics to define meaningful performance changes that translate to real-world driving. Recently, however, research has proposed two composite factors of driving behavior—vehicle control variability and speed—that include metrics like lane positioning, which also have strong face validity as indicators of safe driving (McManus et al., 2024).

Across three sessions, Beeli et al. (2008) tasked 21 participants (20–30 years, all men) to complete a 3-kilometer drive through a city scene with simulated traffic, lights and signs, and pedestrians. The first session was a baseline drive without tDCS. During the other two sessions, the anode and cathode were positioned unilaterally over the DLPFC in a counterbalanced order. Half of the participants randomly received stimulation over the left DLPFC at scalp coordinate F3, while the other half received stimulation over the right DLPFC at scalp coordinate F4. Stimulation was delivered at 1 mA for 15 min offline. Compared to the baseline, participants exhibited fewer speeding violations and maintained greater headway distance when receiving anodal tDCS over the DLPFC compared to cathodal. There were no observable effects of the hemisphere.

Several methodological considerations in this early study must be addressed. Without a sham condition or adequate blinding, it is difficult to disentangle stimulation effects from experimenter influence and participant bias (Boutron et al., 2007). The most common sham procedure ramps up and down the current at the beginning and end of the protocol to mimic initial cutaneous sensations without lasting effects (Woods et al., 2016). Additionally, a between-groups design introduces random variability (Borghini et al., 2014; Lakens, 2013) and fails to account for individual differences in tDCS effects, which can be influenced by anatomical factors (e.g., skull thickness) and behavioral baselines (Bikson et al., 2012; Datta et al., 2012; Horvath et al., 2014; Kim et al., 2014; Li et al., 2015; Opitz et al., 2015; Splittgerber et al., 2020).

TABLE 1 Driving simulators and tDCS summary of studies.

Study	Design	Masking	Sample	Sessions	Current	Duration	Montage (surface area)	Sham	Key results
Beeli et al. (2008)	Mixed groups	Not mentioned	$N = 21$ $n_{F3} = 10$ $n_{F4} = 11$	3	1 mA	15 min offline	Anode: F3 or F4 cathode: ipsilateral mastoid anode: ipsilateral mastoid cathode: F3 or F4 (35 cm^2)	None	Fewer speeding violations and more headway distance from pre-stim to post-stim if anodal than cathodal
Sakai et al. (2014)	Within groups	Single-masked	$N = 13$	3	1.5 mA	20 min online	Anode: F3 and F4 cathode: F4 and F3 (35 cm^2)	30 s ramp up/30 s ramp down	Fewer lane deviations and more accurate headway distance when anodal than cathodal and sham
Facchin et al. (2023)	Within groups	Not mentioned	$N = 27$	3	2 mA	20 min online	Anode: FC4 cathode: Fp1 (35 cm^2) anode: FC4 cathodes: Cp4/FT8/AF4/FCZ (6 cm^2)	10 s ramp up/10 s ramp down	Quicker foot and hand RTs when active than sham; stronger effects when HD than conventional

RTs, reaction times.

Sakai et al. (2014) conducted a sham-controlled, within-groups, single-masked study to address these limitations. Thirteen participants (~35 years, 11 men) were instructed to maintain a specific headway distance from a lead vehicle over a 22-kilometer route. Participants completed this driving task over three testing sessions. In a counterbalanced order, participants received anodal tDCS over the right DLPFC at F4, cathodal tDCS at F4, and sham. Stimulation was set at 1.5 mA for up to 20 min online. There was less variability in headway distance and lane positioning when anodal tDCS was delivered over the DLPFC compared to cathodal and sham. This finding is consistent with research in other domains showing anodal-excitatory effects, but not cathodal-inhibitory effects, for cognitive tasks involving the DLPFC (Jacobson et al., 2012). One explanation could be that the anode likely enhances neuronal firing in active areas, while the cathode may not sufficiently inhibit firing in highly active states.

The neuromodulation field has significantly advanced in the decade since Sakai et al. (2014) published their work. Facchin et al. (2023) explored the effects of different tDCS electrode montages on driving behavior in the latest driving study. Twenty-seven participants (21–30 years, 14 women) completed three 25-min driving sessions while receiving sham tDCS, conventional tDCS, or 4 × 1 HD-tDCS, where four electrodes surround a center electrode of the opposite polarity (Datta et al., 2009; Kuo et al., 2013). Anodal tDCS was applied over the right frontal eye field (FEF) at 1.5 mA over FC4, an area implicated in visuomotor control (Cameron et al., 2015; Grosbras et al., 2005; Nobre et al., 2000). Given that electrode size and material affect spatial resolution, coupled with the structural-functional connectivity of the human brain (Park and Friston, 2013; Sporns, 2013), the DLPFC may have been incidentally targeted during stimulation.

As many can attest, drivers rarely focus on just car following. To this point, Facchin et al. (2023) manipulated driving task difficulty using two variations of stimulus–response detection tasks commonly used in human factors research (Innes et al., 2021). During the drive, the lead car frequently flashed its brake lights, and road signs appeared at random intervals. Participants were asked to brake in response to the lead vehicle and respond to the road signs. Outcomes measured included lane-keeping position, braking reaction time and accuracy, and road sign reaction time and accuracy. Lane maintenance was unaffected by stimulation. Facchin et al. (2023) found that participants responded more quickly, though not more accurately, to the brake lights and road signs when receiving anodal tDCS over the FEF than sham. More prominent effects for these reaction times emerged when stimulation was delivered with HD-tDCS rather than conventional, suggesting heightened response speed to relevant stimuli. Together, these three driving studies indicate that anodal tDCS over the DLPFC may influence distance perception or judgment, observable as changes in distance or faster response times.

2.2 tDCS and flight simulators

Choe et al. (2016) examined the impact of tDCS on skill acquisition and performance across various simulated flight tasks, using scenarios with computer-based simulations that align with Federal Aviation Administration (FAA) Industry Training Standards (FITS) to enhance real-world training relevance (Williams, 2012). Though the performance was tested on flight tasks of varying difficulty, results were only published for the easiest task. Across four sessions, 32 participants (ages 21–64, 31 men) attempted to

TABLE 2 Flight simulators and tDCS summary of studies.

Study	Design	Masking	Sample	Sessions	Current	Duration	Montage (surface area)	Sham	Key results
Choe et al. (2016)	Between groups	Double-masked	$N = 32$ $n_{DLPFC} = 14$ ($n_{active\ DLPFC} = 7$) $n_{M1} = 18$ ($n_{active\ M1} = 10$)	4	2 mA	1 h online	DLPFC anodes: F6/FC6 cathodes: Fp2/AF8/AF4 M1 anodes: Cp1/Cp3 cathodes: Fp1/F8/F9 (15.7 cm^2)	60 s ramp up/60 s ramp down	Smoother landings during sessions 3 and 4 if active than sham over DLPFC only
Mark et al. (2023)	Between groups	Single-masked	$N = 24$ $n_{active} = 12$ ($n_{novice\ active} = 6$) $n_{sham} = 12$ ($n_{novice\ sham} = 6$)	1	1.5 mA	30 min online	Anode: AF8 cathodes: Fpz/T8 (8 cm^2)	30 s ramp up/30 s ramp down	Smoother landings if active than sham; stronger effects for novices than experts
Feltman and Kelley (2024)	Mixed groups	Single-masked	$N = 22$ $n_{online} = 12$ $n_{offline} = 10$	4	2 mA	Online: 2× 10 min Offline: 20 min	Anode: P4 cathode: Fp1 (25 cm^2)	Online 2× 30 s ramp up/30 s ramp down offline 60 s ramp up/60 s ramp down	More likely to follow glide path when active than sham for online only

DLPFC, dorsolateral prefrontal cortex; M1, motor cortex.

replicate a landing demonstrated in an instructional video under daylight conditions with complete visibility. Measured outcomes included landing gravitational force (*g*-force), deviations from flight path, vertical speed, and vertical speed variance. While *g*-force assessment captures landing skill at the most challenging and critical phase of flight, the entire approach is considered with path and vertical speed deviations. Learning rates were measured across sessions, within sessions, and between trials or scenarios (5 trials per session).

Choe et al. (2016) treated stimulation application and location as between-group factors. Half the participants received anodal tDCS (2 mA, 1 h online), while the other half received sham. Stimulation was delivered over the right DLPFC (anodes F6/FC6) or the left motor cortex (anodes CP1/CP3). No significant effects emerged for the motor cortex group. In the DLPFC group, there was less variability in landing *g*-force observed during the third and fourth sessions, suggesting that tDCS may be more beneficial for trained tasks over time. Choe et al. (2016) also collected EEG and functional near-infrared spectroscopy (fNIRS) data that suggests that participants who received active tDCS exhibited altered neuronal activity in the DLPFC and motor cortex compared to those who received sham. Interestingly, behavioral outcomes are commonly observed when delivering anodal excitation over the motor cortex, but not cognitive regions like the DLPFC (Jacobson et al., 2012; Tremblay et al., 2014). The broad influence of the DLPFC on cognitive functions, especially when considering varying stimulation parameters, makes predicting specific behavioral outcomes difficult.

This initial flight study was conducted under relatively simple conditions to facilitate task performance. However, more realistic scenarios may include bad weather, a narrow runway, or auditory distractions. Accordingly, Mark et al. (2023) adjusted the workload during landing. Twenty-four glider pilots (ages 18–22, mostly men) were recruited and categorized as novices or experts based on experience. Participants completed three runs in a single session, with a pre- and post-training run flanking a tDCS run. In the training run, participants received either sham or anodal tDCS over the right DLPFC at AF8 (1.5 mA, 30 min online). Feedback about performance was presented after each trial (72 trials in total). Measures included landing *g*-force, landing descent speed, and flair.

Mark et al. (2023) observed significant stimulation effects only for landing *g*-force. Specifically, participants who received active tDCS compared to those who received sham landed more smoothly when comparing pre-training to training and post-training. This skill-learning effect was more pronounced in novices than experts, similar to findings in electronic sports (Toth et al., 2021), suggesting novices may benefit more from tDCS. The study took place in a functional magnetic resonance imaging (fMRI) machine, revealing that active tDCS than sham increases DLPFC activity and enhances connectivity between the DLPFC and cerebellum, a region involved in error-feedback learning (Doya, 1999).

Targeting other brain regions with tDCS, such as the posterior parietal cortex (PPC), which guides the visuospatial orienting of selective attention (Behrmann et al., 2004; Culham and Valyear, 2006; Kravitz et al., 2011; Lo et al., 2019; Rojas et al., 2018), could clarify the brain-behavior relationship in flight skill acquisition. In the most recent study, Feltman and Kelley (2024) recruited 22 pilots (~37 years, all men) to complete a 90-min round-trip flight while receiving anodal tDCS over the PPC at P4 (2 mA, 20 min total) and sham. Stimulation timing was treated as a between-groups condition between groups. Participants in the offline stimulation group received anodal tDCS (2 mA, 20 min) and sham before flight. Those in the online group received sham and anodal tDCS (2 mA) delivered for 10 min at 30 and 60 min into the flight.

Toward the end of each flight leg, an emergency required participants to disengage autopilot and land safely. Altitude, airspeed, and heading were measured throughout the flight, while glideslope (vertical) and localizer (lateral) deviations were recorded during the approach. Significant effects emerged only for glideslope deviations in the online group, with online anodal tDCS associated with better alignment to the glide path than sham. These findings align with the role of the PPC in visuospatial attention. Together, these flight studies suggest that tDCS over the DLPFC and PPC may enhance landing smoothness, each investigating different aspects of stimulation and simulation parameters.

3 Discussion

Operating a vehicle requires substantial cognitive, perceptual, and motor resources. Non-invasive neuromodulation methods, like tDCS, may offer insights into human performance when cognitive and perceptual enhancement are beneficial. This review synthesizes research on how targeting various brain regions via tDCS can influence outcomes in interactive driving and flight simulators.

Driving studies indicate that anodal tDCS over the DLPFC affects lateral and vertical lane positioning when following a lead vehicle (Beeli et al., 2008; Facchin et al., 2023; Sakai et al., 2014). These findings suggest that tDCS can acutely impact operational (automatic, reactive) and maneuvering (controlled, tactical) driving behaviors (Michon, 1985). It is also likely that tDCS can influence strategic (goal-directed, proactive) driving behaviors, such as trip planning, route memory, or adapting to detours (Michon, 1985). Expanding the complexity of tasks to include strategic and goal-directed elements could be one approach to enhance functional and psychological fidelity, thereby bolstering task realism and immersion (Roberts A. P. J. et al., 2020). Defining meaningful performance benchmarks in driving simulators can further aid in translating research findings into practical, everyday use (McManus et al., 2024).

Similarly, the flight studies demonstrate that anodal tDCS over the DLPFC and PPC is associated with smoother landings, supported by converging neurophysiological evidence from EEG, fNIRS, and fMRI (Choe et al., 2016; Feltman and Kelley, 2024; Mark et al., 2023). Although landing is one of the most challenging tasks for pilots, most of the time spent in flight involves monitoring system controls, including autopilot. For example, future studies may wish to explore the effects of tDCS during monotonous monitoring tasks. This inquiry becomes even more interesting when considering that visual scanning strategies are modulated by expertise (Lefrancois et al., 2016; Lounis et al., 2021). Combining stimulation with multimodal training may enhance its effects (Ward et al., 2017) and contribute further to research on the long-term impacts of tDCS.

Several factors should be carefully considered when interpreting these findings and designing future research. Stimulation protocols must be optimized to reduce individual variability and potential biases. Within-group designs, sham controls, double-masking procedures, and carefully worded materials are some ways to address participant and experimenter biases. It is also critical to address systematic racial bias in neurophysiological research. Most studies in this review recruited small samples of young men, and participants' race or ethnicity was not reported. This omission raises concerns about inclusivity and generalizability, as methods that require adherence between electrodes and the scalp often exclude individuals based on hair type and style (Choy et al., 2022; Parker and Ricard, 2022; Roberts S. O. et al., 2020). Diverse, representative samples are essential to extend research beyond the lab and achieve broader inclusivity.

In summary, tDCS has the potential to modulate brain activity in regions that facilitate vehicle operation on the ground and in the clouds. To deepen our understanding of neuromodulation for human enhancement and continue exploring its possibilities, it is crucial to design stimulation protocols that mitigate biases and conduct studies with tasks or environments that reflect real-world conditions. As the promise of tDCS grows, it is essential to conduct rigorous investigations to fully understand its implications and optimize its application in various contexts.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Evaluating semantic control with transcranial magnetic stimulation: a systematic review with meta-analysis

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Background: This meta-analysis investigates the role of specific brain regions in semantic control processes using Transcranial Magnetic Stimulation (TMS). According to the Controlled Semantic Cognition framework, control processes help manage the contextually appropriate retrieval of semantic information by activating a distributed neural network, including the inferior frontal gyrus, the posterior middle temporal gyrus, and inferior parietal lobule. Lesions in these areas can lead to difficulties in manipulating weakly activated or competing semantic information. Researchers have used TMS to simulate such deficits in healthy individuals.

Method: By synthesizing results from TMS studies that targeted these regions, we aimed to evaluate whether neurostimulation over these areas can effectively impair participants' performance under high semantic control demands.

Results: Results from different meta-analytical approaches consistently showed no significant effects of TMS, especially after correcting for publication bias. Nevertheless, variability in experimental methodologies was evident.

Conclusion: These findings raise questions about the effectiveness of TMS in simulating deficits in semantic control and highlight the need for methodological improvements in future studies to enhance reliability and interpretability.

KEYWORDS

controlled semantic cognition, semantic control, semantic representation, semantic aphasia, transcranial magnetic stimulation

1 Introduction

Over the course of our lives, we acquire an enormous amount of knowledge about the world, including objects, word meanings, facts, and more, which is not tied to any specific time or place – this is referred to as *semantic representation* (Lambon Ralph et al., 2017; Montefinese, 2019; Tulving, 1972). Information within semantic representation can be available to varying degrees, conveying more salient (dominant) or less salient (non-dominant) aspects of meaning (Montefinese, 2019; Vivas et al., 2020). To highlight context- and task-appropriate aspects of meaning, it is often sufficient to automatically retrieve dominant aspects. However, there are occasions when we must focus attention on non-dominant aspects in a controlled manner or selectively retrieve relevant aspects of meaning while inhibiting irrelevant semantic information (Jefferies, 2013). In these instances, semantic control processes play a crucial role. These processes are distinct from the long-term store of semantic knowledge (Jefferies, 2013; Jefferies and Lambon Ralph, 2006; Noonan et al., 2013) and support our ability to efficiently

retrieve and select specific aspects of our semantic representation that are relevant to current goals or context as formulated in the *controlled semantic cognition* (CSC) framework (Lambon Ralph et al., 2017). To borrow an example from Saffran (2000), when thinking about a piano as a musical instrument, keys and pedals (dominant features) are activated automatically. However, in the context of a move, these features become context-irrelevant and must be ignored in favor of features such as weight and size (non-dominant but context-relevant). When the control of semantic information is compromised, individuals lose what Goldstein (1948) called the "abstract attitude" leading to an overreliance on the most immediate and obvious aspects of experience, resulting in deregulated semantic knowledge (i.e., the use of information not pertinent to the context at hand).

This meta-analysis examines over a decade of research using transcranial magnetic stimulation (TMS) to temporarily disrupt control processes in healthy volunteers. It aims to provide causal evidence of the involvement of specific brain regions in these processes, consistent with the CSC framework. In the following sections, this introduction delves into key aspects underpinning our meta-analysis. Section 1.1 provides an in-depth look at the neural mechanisms involved in semantic control, as described by the CSC framework, highlighting the brain regions implicated in control processes. Section 1.2 then explores evidence from neurological patients to illustrate how impairments in semantic control manifest behaviorally and the theoretical perspectives developed to account for these deficits. Section 1.3 introduces the TMS methodology as a tool to investigate semantic control in healthy individuals by creating temporary, controlled disruptions in specific brain regions to simulate patients' semantic control impairments. Indeed, TMS is a powerful tool that, like lesion and neuropsychological studies, helps researchers understand the causal links between brain regions and their functions. Finally, Section 1.4 outlines the aims and rationale of the current meta-analysis, which is to synthesize findings from TMS studies on key semantic control areas to evaluate the reliability of TMS effects on semantic task performance and assess the implications for the CSC framework.

1.1 Neural underpinnings of semantic control processes

According to the CSC framework, semantic cognition activates a distributed neural network (typically left-lateralized), including frontal, temporal, and parietal regions (Binder et al., 2009; Noonan et al., 2013; Jackson, 2021). The distinction between semantic representation and control processes is also reflected in their different brain underpinnings. Semantic representation emerges through learning about the statistical pattern of multimodal experiences with the world. Our knowledge is encoded in modality-specific regions distributed throughout the brain (called 'spokes') (Binder et al., 2016; Martin, 2016), while a single transmodal hub, located bilaterally in the anterior temporal lobes (ATL), coordinates the communication among modality-specific 'spokes', encodes semantic similarity among items, and stores multimodal semantic representations.

Control processes ensure that task- and context-appropriate information is activated within semantic representation (Jefferies, 2013). The CSC theory posits that both the inferior frontal gyrus (IFG) and the posterior middle temporal gyrus (pMTG) serve to regulate performance in semantic tasks by exerting top-down control over the activation of semantic representations in the ATL (Lambon Ralph et al., 2017). The CSC theory also posits that there would be two types of semantic control processes: (a) *controlled retrieval*, which involves identifying and promoting task-relevant but weak aspects of knowledge; and (b) *semantic selection*, which involves dealing with competition between different aspects of knowledge (e.g., different features of a concept). In controlled retrieval tasks, participants must choose a target based on its relation to a cue (Ambrosini et al., 2023). For strong associations, performance is supported by the automatic spread of activation in the semantic network, while additional control resources are required to recover weak associations, e.g., linking DOG with CAT as animals, compared to DOG with SNAKE (Montefinese et al., 2021). In selection tasks, by contrast, participants must select the target related to the cue while ignoring distractors that are task-irrelevant but strongly related to the cue (Almaghyuli et al., 2012; Montefinese et al., 2020). For example, participants could be asked to select the category (e.g., CUTLERY) to which a cue concept (KNIFE) belongs, while inhibiting a distractor strongly associated with the cue (e.g., SHARP) (Montefinese et al., 2020).

Semantic control processes activate regions in the inferior parietal lobe that partially overlap with the multiple-demand network, which is involved in domain-general executive functions (Duncan, 2010). Noonan et al. (2013) suggested that the dorsal angular gyrus and inferior parietal sulcus (henceforth, inferior parietal lobule, IPL) may contribute to semantic control by directing attention to relevant aspects of knowledge for a given task or context. This is achieved through the adaptive coding of task-critical information (Woolgar et al., 2011), similar to how spatial attention is directed to task-relevant locations. However, the role of these regions in semantic control is debated. Recent evidence has failed to find any involvement of the inferior parietal regions in semantic control specifically (Jackson, 2021).

Nevertheless, as mentioned earlier, pMTG and parts of the left IFG specifically support the control of meaning retrieval (Badre et al., 2005; Davey et al., 2016). While the ventral parts of IFG and pMTG seem to be involved in the controlled retrieval of weak information only, the posterior part of IFG appears to be involved when the demands for semantic selection are high (Badre et al., 2005).

1.2 Deficits in semantic control processes in neurological patients

The study of semantic control originated from evidence of deficits observed in neurological patients. Indeed, following the seminal work of Warrington and Shallice (1979), a long tradition of neuropsychological studies on post-stroke patients investigated the deficit in accessing and recovering semantic information (Campanella et al., 2013; Warrington and Mccarthy, 1983). Since then, four main theoretical perspectives have been proposed to explain the behavioral phenomena associated with deficits in semantic access. However, although all of these theories share the theme that, in patients with post-stroke aphasia, semantic representation is intact but the retrieval of information from this representation is impaired (but see also Rapp and Caramazza, 1993), no single existing perspective can account for all of their behavioral phenomena (for a review on the different alternative accounts of behavioral deficits in post-stroke aphasia, see

Mirman and Britt, 2014). In this meta-analysis, we will investigate the roles of specific brain regions implicated in semantic control. We will do so within the CSC framework, which takes into account both the concepts of representation and control and integrates them under the label of semantic cognition. Semantic representation and control can be impaired separately, yielding dissociations between semantic dementia (characterized by degradation of the conceptual representation following anterior temporal lobe atrophy) and semantic aphasia (SA), which is highly relevant for the present work, that results in deficits in semantic control and difficulties in manipulating semantic knowledge in the context of an intact semantic representation (Corbett et al., 2009a; Corbett et al., 2009b; Jefferies and Lambon Ralph, 2006; Rogers et al., 2015). SA patients show inconsistent performance in different semantic tasks that tap the same concepts (Campanella et al., 2013; Jefferies and Lambon Ralph, 2006) and have difficulties in inhibiting dominant distractors or retrieving distant relationships between concepts and less relevant meaning dimensions (Noonan et al., 2013). When asked to name pictures, SA patients show improvement following cues that provide external constraints on retrieval (Corbett et al., 2011; Jefferies et al., 2008b) and exhibit equivalent impairment across modalities when control demands are kept constant (Corbett et al., 2009a; Corbett et al., 2009b; Gardner et al., 2012), indicating that their disorder does not stem from a loss of knowledge, but rather depends on control demands. SA patients perform worse when pictures are presented in related stimulus sets than in unrelated stimulus sets in blocked cyclic paradigms, and this difference increases as the number of stimulus repetitions increases (i.e., a negative serial position effect) (Gardner et al., 2012; McCarthy and Kartsounis, 2000). This results in generally inconsistent performance over repetitions of the same items across several cognitive tasks, highlighting a semantic access disorder rather than an impairment of semantic representation.

Patients with SA are better at retrieving the meaning of highly imageable items (Jefferies et al., 2008a), and they do not show a benefit from concept frequency (Jefferies et al., 2008b). Rather, they often exhibit absent or reverse frequency effects (Almaghyuli et al., 2012; Hoffman et al., 2011): high-frequency words exert greater demands on cognitive control probably because they tend to appear in a broader range of linguistic contexts and have more variable meanings. Finally, the non-semantic executive control deficits in SA patients parallel the problems in the semantic domain (Jefferies and Lambon Ralph, 2006).

1.3 Fundamentals of TMS methodology

The ability of healthy individuals to control semantic retrieval and selection can be disrupted using inhibitory TMS protocols, that is, offline repetitive low-frequency TMS, continuous theta burst TMS, or online multiple-pulse TMS (Beynel et al., 2019). These protocols can induce a so-called virtual lesion in neurologically intact participants. TMS produces focal effects, enabling comparisons of the roles of different brain regions within the same individuals and distinguishing between brain regions that are often damaged together in patients.

When applied over a specific cortical region, a train of high-intensity magnetic pulses can temporarily impair normal functioning of that region. By observing the effects of these changes on behavior or cognitive functions, researchers can infer the causal role of those brain areas. In this respect, TMS technique enables comparisons between the performance of healthy participants under TMS and patients with lesions in areas involved in semantic control. TMS can be administered using different paradigms that align with the two main protocol categories: offline and online stimulation (Beynel et al., 2019). In offline protocols, task performance is evaluated before and after TMS administration. In online protocols, TMS stimulation is applied at specific time points while participants are engaged in a cognitive task, and the immediate effect on their performance is assessed. Furthermore, TMS experimental designs employ two basic types of control conditions. To test the neuroanatomical specificity of a region, available methods include: (i) stimulating a site unrelated to the function being studied, (ii) using a sham stimulation condition that mimics TMS nonspecific effects without inducing any neural modulation, and (iii) using a no-stimulation condition, which represents a weaker control as it does not account for the sensory confounds of TMS conditions. To assess the function of a specific region, (iv) the control task (or condition) method is more effective. This involves comparing the effects of TMS on experimental and control tasks, with the prediction that TMS should affect the target task involving the cognitive process of interest but not the control task (Jahanshahi and Rothwell, 2000).

1.4 The present study

To simulate the deficits observed in SA patients, several studies have applied TMS on healthy volunteers to temporarily inhibit activity in specific brain regions, including the IFG, pMTG, and IPL (Davey et al., 2015; Hoffman and Crutch, 2016;Hallam et al., 2016; Häuser et al., 2016; Krieger-Redwood and Jefferies, 2014; Medaglia et al., 2018, 2021; Teige et al., 2018; Whitney et al., 2011, 2012; Zhang et al., 2019). These TMS interventions were designed to assess their impact on semantic control task performance in a controlled experimental context. However, despite the increasing number of TMS studies, a comprehensive systematic review is still lacking. TMS effects tend to be subtle, studies are often underpowered, and findings may not consistently replicate across different laboratories. Thus, the question remains: Do inhibitory TMS protocols reliably induce significant performance decline in demanding semantic decisions among healthy volunteers, consistent with CSC predictions? To address this question, we conducted a meta-analysis of all existing TMS studies targeting the IFG, pMTG or IPL. We did this within the CSC framework, which takes into account both the concepts of representation and control and integrates them under the label of semantic cognition.

2 Method

This meta-analysis was not registered, and no protocol was prepared. However, it adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021a, 2021b). Various strategies were used to find relevant articles and then several criteria were applied to determine whether a study could be included in the meta-analysis.

2.1 Search for the literature

A computer-based search was performed using the electronic bibliographic databases PubMed, Scopus, Web of Science, and

PsycInfo for articles containing the following terms in their title, abstract, or keywords: ("*semantic cognition*" *OR* "*semantic control*" *OR* "*semantic selection*" *OR* "*controlled retrieval*") *AND* (*TMS OR* "*transcranial magnetic stimulation*" *OR TBS OR* "*theta burst stimulation*"). It should be noted that literature search on PubMed was limited to titles and abstracts, as keywords cannot be included in the search. The search was limited to peer-reviewed articles published up to August 2024. Further candidate studies were identified by checking the reference lists of reports that passed the screening process and those of previous reviews and meta-analyses on semantic control processes (Hoffman and Morcom, 2018; Jackson, 2021; Mirman and Britt, 2014; Lambon Ralph et al., 2017; Noonan et al., 2013).

2.2 Eligibility criteria

Different eligibility criteria were used according to the prespecified hierarchy detailed in what follows.

1 Only primary studies reporting original results were included (e.g., no reviews or meta-analyses). Moreover, only studies collecting and analyzing quantitative data that were published in peer-reviewed journals and were available in English were considered. Other eligibility criteria were assessed using the PICO framework (Patient, Intervention, Comparison, Outcome) (Schardt et al., 2007), as follows.
2 (Population): we included studies on healthy adult participants (18 years of age or older);
3 (Intervention): we included studies using inhibitory TMS to cause a virtual lesion (see above), with the TMS targeting the IFG and/or pMTG and/or IPL;
4 (Comparison): we considered studies employing an experimental design that included at least a dual contrast (i.e., at least a 2-factor statistical design) to control for (i) the specific effect of TMS stimulation (ii) on semantic control ability. In other words, we considered studies (i) contrasting a condition with the inhibitory TMS with at least one TMS-related control condition (no TMS, or sham simulation, and/or TMS stimulation over a control site) (ii) on semantic control processes (i.e., contrasting a condition with high semantic control requirements with a condition with low semantic control requirements and/or a non-semantic control task). To determine the conditions with high semantic control requirements, we adopted the same contrasts employed in Jackson's (2021) meta-analysis. Across all these contrasts, the level of semantic control required varied in several ways: (a) Some tasks emphasized subordinate or less frequent aspects of meaning (e.g., weaker associations, subordinate homonyms). (b) Other tasks demanded inhibition of prepotent responses or increased interference from competitors (e.g., more distractors or greater similarity to distractors). (c) Certain tasks focused on resolving incongruent meanings or ambiguity (e.g., semantic violations, homonym ambiguity). (d) Some tasks intentionally reduced contextual support for determining meaning (e.g., context surprisal, unpredictability). (e) Finally, specific tasks required flexible switching between different meanings or contexts (e.g., alternative uses of task, or switching instructions);
5 (Outcome): we considered the studies testing the specific TMS-induced increase of the semantic control-related effects (i.e., a performance worsening when semantic control requirements were higher) on participants' response times, which are a more sensitive measure of TMS-induced detrimental effects on participants' cognitive performance (which are assumed to be caused by a disturbance in the normal functioning of the stimulated region, rather than its inactivation; Pascual-Leone et al., 2000).

2.3 Study selection

In our meta-analysis, one author (EA) performed the electronic database searches and the first round of screening to exclude duplicate records. Subsequently, the reports (full-text articles) for the resulting unique records (see Figure 1) and those identified via citation searching were retrieved and two authors (EA and MM) independently assessed them to determine their eligibility. In cases of disagreement between the two reviewers, a third reviewer (SBV) was there to solve them. Notably, no discrepancies arose between the initial screeners (EA and MM).

2.4 Data extraction

The effectiveness of TMS over the IFG, pMTG, or IPL in disrupting semantic control processes was investigated by comparing participants' semantic control ability across different conditions. Specifically, the experimental effects were measured as the difference in response times between a high semantic control condition and at least one control condition/task with no or low semantic control demands (as detailed above). These differences were then compared between the active TMS condition and a control condition (e.g., no TMS, sham TMS, or TMS applied to a control site). The resulting outcome thus reflects the interaction between the specific TMS effects and the varying levels of semantic control requirements, with positive values indicating that TMS decreased semantic control (i.e., increased the performance cost in high semantic control conditions).

For the statistical assessment of the participants' specific semantic control-related effects, we considered the effects tested by employing either (1) a 2-level SCP (semantic control process) factor, contrasting conditions with higher vs. lower semantic control requirements within the same experimental task; (2) a 2-level TASK factor, contrasting a task with semantic control requirements with a non-semantic task; (3) both SCP and TASK factors (i.e., an SCP × TASK interaction). To ensure using the best estimation of the specific semantic control-related effects, whenever possible we preferred to extract the effects derived from the SCP × TASK interaction, assuring a better control of unspecific performance effects, followed by the SCP factor, providing a more direct effect over the TASK factor, which in turn provides the least control of the specific semantic control-related effects. Moreover, for the statistical assessment of the specific TMS-related effects, we considered the effects tested by employing either (1) a 2-level TMS factor, contrasting the active TMS condition with either a no-TMS or a sham stimulation condition; (2) a 2-level SITE factor, contrasting the active TMS condition over one of the brain regions of interest (i.e., IFG, pMTG, and IPL) and the same TMS stimulation over a control site (e.g., the vertex); (3) both TMS and SITE factors (i.e., a TMS × SITE interaction). To ensure using the best estimation of the specific TMS-related effects,

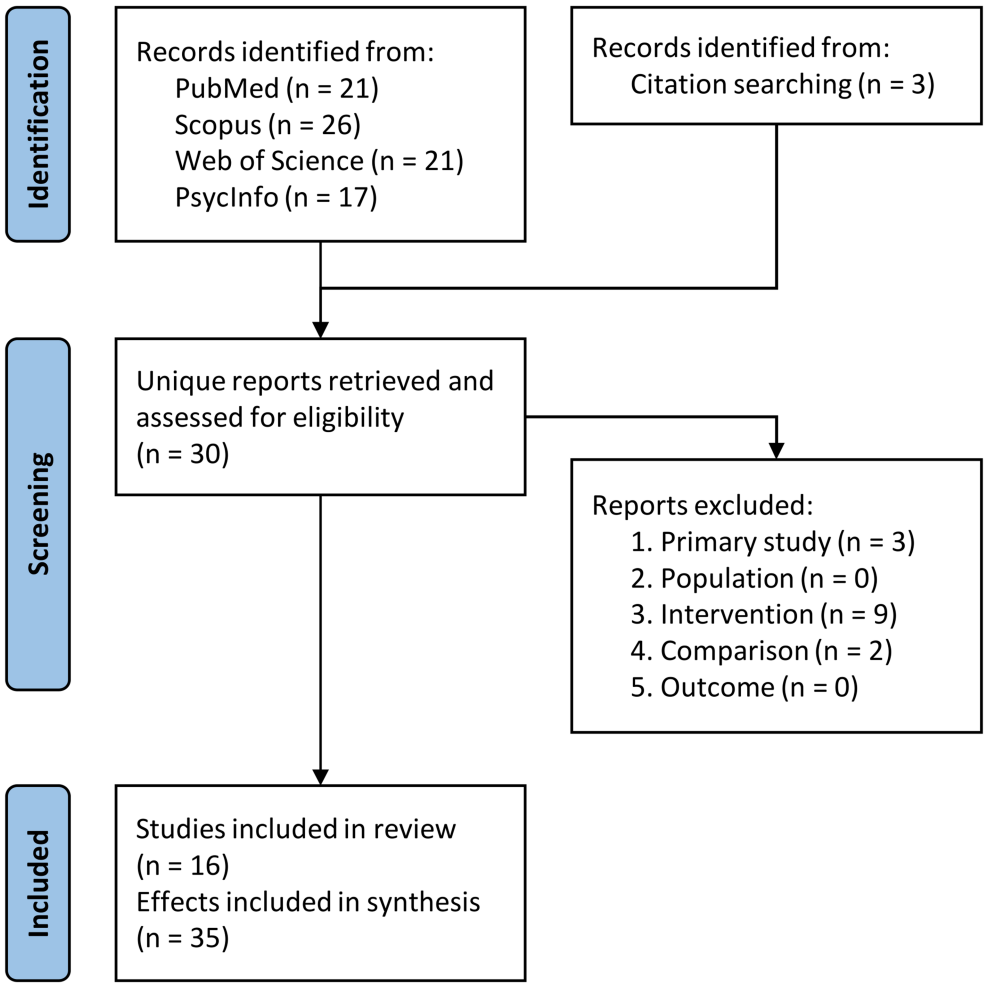

FIGURE 1
Flow chart of the selection process for the included studies. See the main text for the description of the exclusion criteria.

whenever possible we preferred to extract the effects derived from the TMS × SITE interaction, assuring a better control of unspecific TMS effects, followed by the SITE factor, providing a more controlled effect over the TMS factor, which in turn provides the least control of the TMS-specific effects. Therefore, the effects of interest derived from at least a 2 × 2 interaction between a TMS/SITE factor and an SCP/TASK factor, and at best a 2 × 2 × 2 × 2 TMS × SITE × SCP × TASK interaction. When the eligible studies employed a different statistical design (e.g., using a 3 × 2 design to contrast a semantic control-related effect–derived from conditions with higher vs. lower semantic control requirements–across three TMS conditions–active TMS vs. no TMS vs. TMS over a control site) we followed the prespecified hierarchy we just described to extract the 2 × 2 SITE × SCP effect.

When multiple experimental effects of interest were reported (e.g., when TMS was administered at multiple active sites, or when more semantic control tasks were performed), all of them were extracted and included in our meta-analytic models.

For each included effect, two authors (MM and EA) independently extracted the relevant outcome data for the statistical comparison reflecting the experimental effects of interest. In doing this, we again followed a prespecified hierarchy: When available, the F statistics (or the T statistics) and related degrees of freedom were extracted (and used to compute the corresponding exact *p*- and *z*-values) for the statistical comparisons described above. When these statistics were not available, the means (M) and standard deviations (SD) were extracted for the outcome of interest. Specifically, we extracted the mean (and related SD) of the difference between high vs. low/no semantic-control scores for both the active TMS group/condition and the control/sham groups/conditions (M1 and SD1 and M2 and SD2, respectively) as a measure of the semantic control performance. If SD were unavailable, standard errors (SE) were extracted. When these data were presented only as graphs, *WebPlotDigitizer*[1] was used to extract M and SD/SE estimates from the available graphs.

Based on these outcome data, we computed the corresponding effect sizes (Hedge's *g*, a standardized mean difference which is equivalent to the bias-corrected version of Cohen's *d*) for the effects of interest, as well as the corresponding sampling variance (V), SE and 95% confidence interval ($CI_{95\%}$). Positive *g* values indicated a

1 https://automeris.io/WebPlotDigitizer/

TMS-dependent increase of the performance cost in the conditions with higher vs. lower semantic control requirements, that is, a TMS-dependent impairment in semantic control ability. For within-participants designs, computing the *g* (and *d*) requires taking into account the correlation (*r*) between the two repeated-measure semantic control-related effects (M1 and M2), because the pooled SD is computed as the square root of ($SD1^2 + SD2^2 – 2 \times r \times SD1 \times SD2$). However, this *r* value was never reported in the included within-participants studies, so we conservatively chose to use a value of $r = 0.5$. However, we also performed a sensitivity analysis by replicating all the analyses using the values $r = 0$, 0.25, and 0.75. The effect size and variance calculation were performed using R and the functions *escalc* and *vcalc* from the *metafor* package.

For each included effect, two authors (MM and EA) independently extracted the information about the corresponding report, the sample size used in the statistical analyses, the study design, the type of task or TMS control contrast, the TMS stimulation parameters, and the analyses and outcomes. Any discrepancies were solved by discussion.

2.5 Data analysis

2.5.1 Risk of bias assessment

Following the Cochrane guidelines (Higgins et al., 2011), the methodological quality of the studies was assessed using the RoB-2 tool (Sterne et al., 2019). The tool is structured into six domains through which bias could be introduced into the outcome. These were identified based on empirical evidence and theoretical considerations. Because the domains cover all types of bias that may affect experimental results, each domain is mandatory, and no additional domains should be added. The six domains are: (1) bias arising from the randomization process; (2) bias due to period or carryover effects; (3) bias due to deviations from intended interventions; (4) bias due to missing outcome data; (5) bias in the measurement of the outcome; and (6) bias in the selection of the reported result. For instance, the following signaling questions are used to determine the risk of bias for each domain: (1) "Was the allocation sequence concealed until participants were enrolled and assigned to interventions?"; (2) Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period? (3)"Were participants aware of their assigned intervention during the trial?"; (4) "Were data for this outcome available for all, or nearly all, participants randomized?"; (5) "Was the method of measuring the outcome inappropriate?"; and (6) "Were the data that produced this result analyzed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?

For each category of risk, two investigators (MM and EA) independently answered multiple questions for each domain with a 5-level multiple choice answer (yes, probably yes, no, probably no, and no information). Any discrepancies were solved by discussion. The RoB 2 tool included an algorithm for automatic calculation of the domain-specific level of bias and for overall bias. A study was characterized with a low risk of bias when all domains were considered to have a low risk of bias; with some concerns when at least one domain took a "some concerns" evaluation; with a high risk of bias when at least one domain was considered to have a high risk of bias or when at least three domains took a "some concerns" evaluation. It is important here to note that we did not include the domain of the randomization process in assessing the overall risk of bias, because the use of TMS makes it practically impossible to prevent investigators and participants from knowing the allocated intervention (e.g., experimental vs. sham or no stimulation); therefore, most of the included studies (13 out of 16) would have been rated with a high risk of bias due to this issue.

2.5.2 Risk of publication bias

There are several methods to assess the presence of publication bias. Publication bias was first examined with a funnel-plot-based method for the effect sizes, and the eventual presence of this bias was then corrected by using the trim-and-fill method (Duval and Tweedie, 2000). To test for potential small study bias, we also examined the presence of funnel plot asymmetry using the rank test and the Egger's regression test (Egger et al., 1997). In the funnel plot, more precise estimates are located at the top near the combined effect size, whereas less precise estimates are located at the base of the funnel plot. If there is no publication bias, the studies would be expected to be symmetrically distributed on both sides of the combined effect size line. In case of publication bias, the funnel plot may be asymmetric since the absence of studies would distort its distribution on the graph. The trim-and-fill method examines this asymmetry and, with a rank-based data augmentation procedure, estimates the number and location of missing studies, adjusting for the possible effects of missing studies. If the conclusion of the meta-analysis remains unchanged after adjustment for publication bias, the results can be considered reasonably robust, excluding publication bias.

However, the trim-and-fill method only corrects for publication bias based on observed effect size and not based on whether an effect was significant (Simonsohn et al., 2014), and it does not yield corrected meta-analytic effect size estimates that are close to the true effect size when publication bias is based on the *p*-value of the study (Peters et al., 2007; Terrin et al., 2003). Therefore, we further examined publication bias using selection models based on the *p*-values of the included studies (Hedges, 1992; Iyengar and Greenhouse, 1988; Vevea and Hedges, 1995). These selection models use weighted distributions to estimate the probability that non-significant studies were included in the meta-analysis (the publication bias) based on the average effect estimate. If non-significant results are less likely to be published than significant ones, this approach produces an adjusted average effect estimate that accounts for the estimated publication bias by giving more weight to the studies included in the intervals with lower publication probability (which are usually the non-significant ones). Selection models also have the advantage of working well even under high heterogeneity (Carter et al., 2019) and are based on a well-founded model of the publication process and how publication bias actually occurs (i.e., research studies are selected for publication based on the observed statistical significance; Ferguson and Heene, 2012; Masicampo and Lalande, 2012). We initially specified a two-sided selection using p-value cutoffs driving publication bias for significant and marginally significant studies as $p = 0.05$ and 0.1. We also used the selection model to test for publication bias by comparing the unadjusted and selection model using a likelihood ratio test. We used both frequentist selection models and a robust Bayesian meta-analysis (RoBMA, Maier et al., 2023) that combine selection models to model averaging (for details on Bayesian model averaging, see Gronau et al., 2017).

Finally, publication bias was examined using the *z*-curve analysis (Bartoš and Maier, 2020) on the z scores computed from the extracted *p*-values of the included effects, using the *zcurve* R package (Bartoš and Maier, 2020; Bartoš and Schimmack, 2020; Schimmack and Brunner, 2017). The *z*-curve analysis also relies on assumptions about how the *p*-values (transformed into *z* values) distribute, that is, the fact that publication bias should give results characterized by an unusually large proportion of *p*-values that fall just below the 0.05 significance level (Bartoš and Schimmack, 2020). It also explicitly incorporates a random effect model (and thus can handle effect sizes heterogeneity) using a mixture of *z* distributions (Brunner and Schimmack, 2020). Furthermore, the *z*-curve provides two power estimates that allow a better estimate the replicability of the included studies (Bartoš and Schimmack, 2022): (1) the conditional average power of the studies yielding significant effects, called the expected replication rate (ERR), which is equivalent to the *p*-curve power estimate, and (2) the unconditional average power of the studies in the literature, called the expected discovery rate (EDR), which is the overall probability of obtaining significant effects when both significant and non-significant results are present in a literature. When this estimate is compared with the Observed Discovery Rate (ODR), that is, the proportion of statistically significant results within the z-curve analysis, an indicator of publication bias is obtained.

2.5.3 Meta-analyses

The meta-analyses were conducted using the *RoBMA* package (Bartoš and Maier, 2020) in JASP and the *metafor* package in R using a restricted maximum-likelihood estimator method. They were based on the Hedge's *g* effect size (and related SE and V) for the comparison of the TMS-dependent change in semantic control-related performance between the active and control TMS groups/conditions, as described above (see Data extraction).

In order to achieve maximum statistical power, we chose to use all the available effects of interest in the included studies, as noted above (see Data extraction). However, multiple effects extracted from the same study are expected to be more similar to each other than effects from different studies. Ignoring this effect size dependency tends to underestimate SE, which in turn results in an inflated type-I error rate (Hedges, 2009). Therefore, we performed a three-level random effects model using the *rma.mv* function, which models three sources of variance to account for effect size dependency, which was also performed with a cluster-robust variance estimation method using the *robust* function and the *clubSandwich* package (for more details, see Assink and Wibbelink, 2016; Assink and Wibbelink, 2023).

The random effects model allows evaluating the presence of publication bias with the rank test, but it does not provide tools to evaluate (and correct) the impact of the potential publication bias on the combined effect size resulting from the research synthesis. Therefore, we also employed other meta-analytical approaches (see below) that allowed us to do that, but without taking into account effect size dependency, after having performed a likelihood ratio test to verify whether the inclusion of the study grouping variable (to estimate the random variation between effect sizes from the same study and thus account for the effect sizes dependency) was justified.

First, a classical frequentist model was fitted using a random model, providing standard methods to evaluate the impact of publication bias (that is, the funnel plot with the trim-and-fill method in case of asymmetry, evaluated with the rank test and the Egger's test). We then performed a frequentist meta-analysis using a two-sided selection model with one-tailed *p*-value cutoffs of 0.05 and 0.1 to evaluate the presence of heterogeneity and to evaluate and correct for the impact of selection bias around statistical significance (Vevea and Woods, 2005). This frequentist meta-analysis was complemented by a robust Bayesian meta-analysis calculated with the RoBMA package (Bartoš and Maier, 2020). Bayesian meta-analysis has the advantage of providing probabilities for the experimental and null hypotheses and additional tests for heterogeneity, as well as publication bias. As prior distributions, we used a normal distribution for the effect size ($\mu = 0$, $\sigma = 1$), an inverse gamma distribution for heterogeneity ($\alpha = 1$, $\beta = 0.15$), and the cumulative sum of the Dirichlet distribution ($\alpha = 1,1$) for the two-interval selection model (with one-tailed p-value cutoffs of 0.05 and 0.1 for non-significant studies). Null priors were spike functions at 0. The study heterogeneity was then determined using standard measures (that is, the *Q* test and τ).

3 Results

3.1 Overview

The screening process sequence is depicted in the PRISMA flowchart (Figure 1). Initially, our literature search yielded a total of 85 records, of which 27 were unique records (i.e., after removing duplicates). Three additional articles were identified via citation searching. The resulting 30 full-text articles were retrieved and underwent full-text review. Ultimately, 16 studies met our inclusion criteria, involving a combined sample of 313 participants. These studies investigated a total of 35 effects (for a total sample of 688 participants), accounting for cases where the experimental design allowed to extract multiple effects (Davey et al., 2015; Häuser et al., 2016; Hoffman et al., 2012; Hoffman and Crutch, 2016; Medaglia et al., 2018, 2021; Timofeeva et al., 2024) or when multiple stimulation sites were used (Davey et al., 2015; Krieger-Redwood et al., 2014; Timofeeva et al., 2024; Wawrzyniak et al., 2017; Whitney et al., 2011, 2012; Zhang et al., 2019; Zhao et al., 2021). Note that a power analysis performed with the *metapower* R package revealed that our sample size (35 effects with a study size of $n = 20$) ensured a statistical power of about 80% to find an expected small/medium effect size of 0.35 with a random effect model, assuming a moderate/substantial heterogeneity ($I^2 = 0.60$).

Response times served as the dependent variable across all studies, with 2 employing a between-participants design and 14 using a within-participants design. As regards the TMS stimulation protocols, the studies exhibited considerable homogeneity. Regarding the timing of stimulation, 3 studies targeted brain areas during task performance (i.e., online stimulation), while 13 targeted brain areas before the task (i.e., offline stimulation). The stimulation paradigms varied: of the 3 studies employing online TMS, 1 used triple-pulse TMS (40 Hz) (Zhang et al., 2019) and 2 used double-pulse TMS (25 Hz and 40 Hz, respectively, Teige et al., 2018, Zhao et al., 2021); of the 13 studies employing offline TMS, 9 used repetitive low-frequency TMS (1 Hz) (Häuser et al., 2016; Hoffman et al., 2010, 2012; Hoffman and Crutch, 2016; Krieger-Redwood and Jefferies, 2014; Davey et al., 2015; Whitney et al., 2011, 2012) and 4 used continuous theta burst TMS (3 50–Hz pulses at 5 Hz) (Medaglia et al., 2018, 2021; Timofeeva et al., 2024; Wawrzyniak et al., 2017). Brain regions of interest were localized on structural T1-weighted MRI scans for all participants. See Table 1 for more details.

TABLE 1 Characteristics of the studies included in this meta-analysis.

Study ID	DOI	Effect ID	Stimuli	Task	SCP type[a]	TMS protocol	Site	TMS intensity	TMS parameters	Design	Extracted effect	n
1	10.1523/JNEUROSCI.3783-10.2010	1	Words	Synonym judgment	c, d	rTMS, offline	l IFG	120% rMT (by eye)	1 Hz, 600 s	WTN, 3 × 2 × 2	TMS × SCP × TASK	13
2	10.1093/cercor/bhq180	2	Words	Association task	a	rTMS, offline	l IFG	120% aMT (by eye)	1 Hz, 600 s	WTN, 3 × 2 × 2 × 2	TMS × SITE × SCP × TASK	16
		3	Words	Association task	a	rTMS, offline	l pMTG	120% aMT (by eye)	1 Hz, 600 s	WTN, 3 × 2 × 2 × 2	TMS × SITE × SCP × TASK	16
3	10.1080/02687038.2011.608838	4	Pictures	Association task	b	rTMS, offline	l pMTG	120% rMT (by eye)	1 Hz, 600 s	WTN, 2 × 3 × 2	TMS × SITE × TASK	14
		5	Words	Association task	b	rTMS, offline	l pMTG	120% rMT (by eye)	1 Hz, 600 s	WTN, 2 × 3 × 2	TMS × SITE × TASK	14
4	10.1162/jocn_a_00123	6	Words	Association task	b	rTMS, offline	l IFG	120% aMT (by eye)	1 Hz, 600 s	WTN, 3 × 2 × 5	TMS × SITE × TASK	16
		7	Words	Association task	b	rTMS, offline	l pMTG	120% aMT (by eye)	1 Hz, 600 s	WTN, 3 × 2 × 5	TMS × SITE × TASK	16
		8	Words	Association task	b	rTMS, offline	l IPL	120% aMT (by eye)	1 Hz, 600 s	WTN, 3 × 2 × 5	TMS × SITE × TASK	16
5	10.1016/j.neuropsychologia.2014.09.014	9	Pictures	Cycling picture naming	b	rTMS, offline	l IFG	120% rMT (by eye)	1 Hz, 600 s	WTN, 2 × 2 × 2 × 6	TMS × SCP	16
		10	Pictures	Cycling picture naming	b	rTMS, offline	l pMTG	120% rMT (by eye)	1 Hz, 600 s	WTN, 2 × 2 × 2 × 6	TMS × SCP	16
6	10.1523/JNEUROSCI.4705-14.2015	11	Word-picture	Word-picture matching	a	rTMS, offline	l pMTG	120% aMT (by eye)	1 Hz, 600 s	WTN, 3 × 4 × 2	TMS × SCP	18
		12	Word-picture	Word-picture matching	a	rTMS, offline	l IPL	120% aMT (by eye)	1 Hz, 600 s	WTN, 3 × 4 × 2	TMS × SCP	18
		13	Word-picture	Identity-matching task	b	rTMS, offline	l pMTG	120% aMT (by eye)	1 Hz, 600 s	WTN, 3 × 4 × 2	TMS × SCP	18
		14	Word-picture	Identity-matching task	b	rTMS, offline	l IPL	120% aMT (by eye)	1 Hz, 600 s	WTN, 3 × 4 × 2	TMS × SCP	18
7	10.1016/j.neuropsychologia.2016.09.012	15	Words	Feature selection	b	rTMS, offline	l IFG	100% aMT (by eye)	1 Hz, 600 s	WTN, 3 × 2	SITE × SCP	18
8	10.1016/j.neuropsychologia.2016.09.003	16	Sentences	Meaningfulness judgment	a	rTMS, offline	l IFG	110% aMT (by eye)	1 Hz, 600 s	WTN, 2 × 2 × 2	SITE × SCP	16
		17	Sentences	Meaningfulness judgment	a	rTMS, offline	l IFG	110% aMT (by eye)	1 Hz, 600 s	WTN, 2 × 2 × 2	SITE × SCP	16
9	10.1016/j.cortex.2015.11.021	18	Words	Taxonomic judgment	b	rTMS, offline	r IPL	65% max output	1 Hz, 600 s	WTN, 3 × 2 × 2	TMS × SITE × SCP	18
		19	Words	Synonym judgment	b	rTMS, offline	r IPL	65% max output	1 Hz, 600 s	WTN, 3 × 2 × 2	TMS × SITE × TASK	18
10	10.1371/journal.pone.0177753	20	Sentences	Lexical decision	d	cTBS, offline	l IFG	80% aMT (MEP)	3 50-Hz pulses at 5 Hz	WTN, 3 × 4	TMS × SCP	19
		21	Sentences	Lexical decision	d	cTBS, offline	l pMTG	80% aMT (MEP)	3 50-Hz pulses at 5 Hz	WTN, 3 × 4	TMS × SCP	19
11	10.1523/JNEUROSCI.0092-17.2018	22	Words/sentences	Verb generation/sentence completion	a	cTBS, offline	l IFG	80% aMT (by eye)	3 50-Hz pulses at 5 Hz	BTN, 2 × 2 × 2	TMS × SITE × SCP	28
		23	Words/sentences	Verb generation/sentence completion	a	cTBS, offline	l IFG	80% aMT (by eye)	3 50-Hz pulses at 5 Hz	BTN, 2 × 2 × 2	TMS × SITE × SCP	28
12	10.1016/j.cortex.2018.03.024	24	Words	Association task	a	dbTMS, online	l pMTG	60% max output	25 Hz	WTN, 2 × 3 × 4	TMS × SCP	15
13	10.1002/hbm.24781	25	Words	Association task	b	tbTMS, online	l IFG	100% rMT (MEP)	40 Hz	WTN, 4 × 2	SITE × TASK	24

(Continued)

10.3389/fpsyg.2024.1435338

10.3389/fpsyg.2024.1435338

TABLE 1 (Continued)

Study ID	DOI	Effect ID	Stimuli	Task	SCP type[a]	TMS protocol	Site	TMS intensity	TMS parameters	Design	Extracted effect	n
		26	Words	Association task	b	tbTMS, online	l pMTG	100% rMT (MEP)	40 Hz	WTN, 4 × 2	SITE × TASK	24
		27	Words	Association task	b	tbTMS, online	r IPL	100% rMT (MEP)	40 Hz	WTN, 4 × 2	SITE × TASK	24
14	10.1523/ENEURO.0382-20.2021	28	Sentences	Sentence completion	a	cTBS, offline	l IFG	80% aMT (by eye)	3 50-Hz pulses at 5 Hz	BTN, 2 × 2 × 2	TMS × SITE × SCP	41
		29	Words	Word generation	a	cTBS, offline	l IFG	80% aMT (by eye)	3 50-Hz pulses at 5 Hz	BTN, 2 × 2 × 2	TMS × SITE × SCP	41
15	10.1523/JNEUROSCI.1355-21.2021	30	Videos	Gender voice discrimination	c, d	dbTMS, online	l IFG	50% max output	40 Hz	WTN, 3 × 2 × 2 × 8	SITE × SCP	26
		31	Videos	Gender voice discrimination	c, d	dbTMS, online	l pMTG	50% max output	40 Hz	WTN, 3 × 2 × 2 × 8	SITE × SCP	26
16	10.1093/cercor/bhae188	32	Pictures	Cued picture naming	e	cTBS, offline	l pMTG	80% aMT (by eye)	3 50-Hz pulses at 5 Hz	WTN, 2 × 2 × 3	SITE × SCP	15
		33	Pictures	Cued picture naming	e	cTBS, offline	l IPL	80% aMT (by eye)	3 50-Hz pulses at 5 Hz	WTN, 2 × 2 × 3	SITE × SCP	15
		34	Pictures	Cued picture naming	e	cTBS, offline	l pMTG	80% aMT (by eye)	3 50-Hz pulses at 5 Hz	WTN, 2 × 2 × 3	SITE × SCP	14
		35	Pictures	Cued picture naming	e	cTBS, offline	l IPL	80% aMT (by eye)	3 50-Hz pulses at 5 Hz	WTN, 2 × 2 × 3	SITE × SCP	14

[a] Type of manipulations of the semantic control process (SCP) requirements (see Section 2.2); TBS, theta-burst stimulation; dpTMS, double-pulse TMS; tpTMS, triple-pulse TMS; l and r, left and right hemisphere; rMT and aMT, resting and active motor threshold; WTN, within-ss design; BTW, between-ss design; n, size of the sample used in the reported.

The tasks meeting inclusion criteria involved manipulations related to semantic ambiguity (Hoffman et al., 2010), competitor interference (Krieger-Redwood and Jefferies, 2014; Davey et al., 2015; Hoffman et al., 2012; Hoffman and Crutch, 2016; Whitney et al., 2012; Zhang et al., 2019), association strength (Hallam et al., 2016; Teige et al., 2018; Whitney et al., 2011), semantic violations (Wawrzyniak et al., 2017; Zhao et al., 2021), meaning dominance (Davey et al., 2015; Häuser et al., 2016; Medaglia et al., 2018, 2021), and context switching (Timofeeva et al., 2024). These manipulations were applied to words (Davey et al., 2015; Hoffman et al., 2010; Hoffman and Crutch, 2016; Medaglia et al., 2018; Teige et al., 2018; Whitney et al., 2011, 2012; Zhang et al., 2019), sentences (Häuser et al., 2016; Medaglia et al., 2018, 2021; Wawrzyniak et al., 2017), pictures (Davey et al., 2015; Hoffman et al., 2012; Krieger-Redwood and Jefferies, 2014; Timofeeva et al., 2024), and videos (Zhao et al., 2021).

3.2 Risk of bias assessment

The risk of bias for the selected studies was assessed based on the effects obtained from the data analysis performed in this meta-analysis. Our analysis revealed that the risk of bias must be interpreted cautiously. Indeed, it is important here to reiterate that, if we had included the domain related to the randomization in the overall bias evaluation, most studies would have been rated as having a high risk of bias. This is because only three studies (Timofeeva et al., 2024; Zhang et al., 2019; Zhao et al., 2021) were deemed to have a "low risk" of bias in the randomization domain. These studies ensured that participants were unaware of the intervention assignments by using a control condition (e.g., the vertex of the head) that matched the physical sensations of the experimental intervention.

When the randomization domain was excluded from the overall evaluation, only one out of 16 studies (Häuser et al., 2016) had a "high risk" of bias due to concerns about selective reporting of results. The remaining 15 studies had "some concerns" in this domain because most authors had not prepublished their statistical analysis plan. The summary of the assessment performed in each of the six domains is given in Figure 2.

3.3 Results of synthesis and publication bias

We first present the results of the classical frequentist meta-analysis, which provides the standard methods to estimate the presence of publication bias. The effect sizes (and their standard error) for the comparison of the TMS-dependent change in semantic control performance between the active and control TMS groups/conditions are displayed in a funnel plot in Figure 3. Hedges' g values for the included effects ranged from −0.80 to 1.05. The combined effect estimated by the random model was 0.111, with the $CI_{95\%}$ ranging from −0.026 to 0.248 ($Z = 1.592$, $p = 0.111$; see Figure 2). There appeared to be substantial heterogeneity among the true effects [$Q(34) = 104.54$, $p < 0.001$], suggesting that the effects of interest may differ widely across studies ($\tau = 0.341$).

The three-level random effects models confirmed these results, with an estimated combined effect of 0.123, with the $CI_{95\%}$ ranging

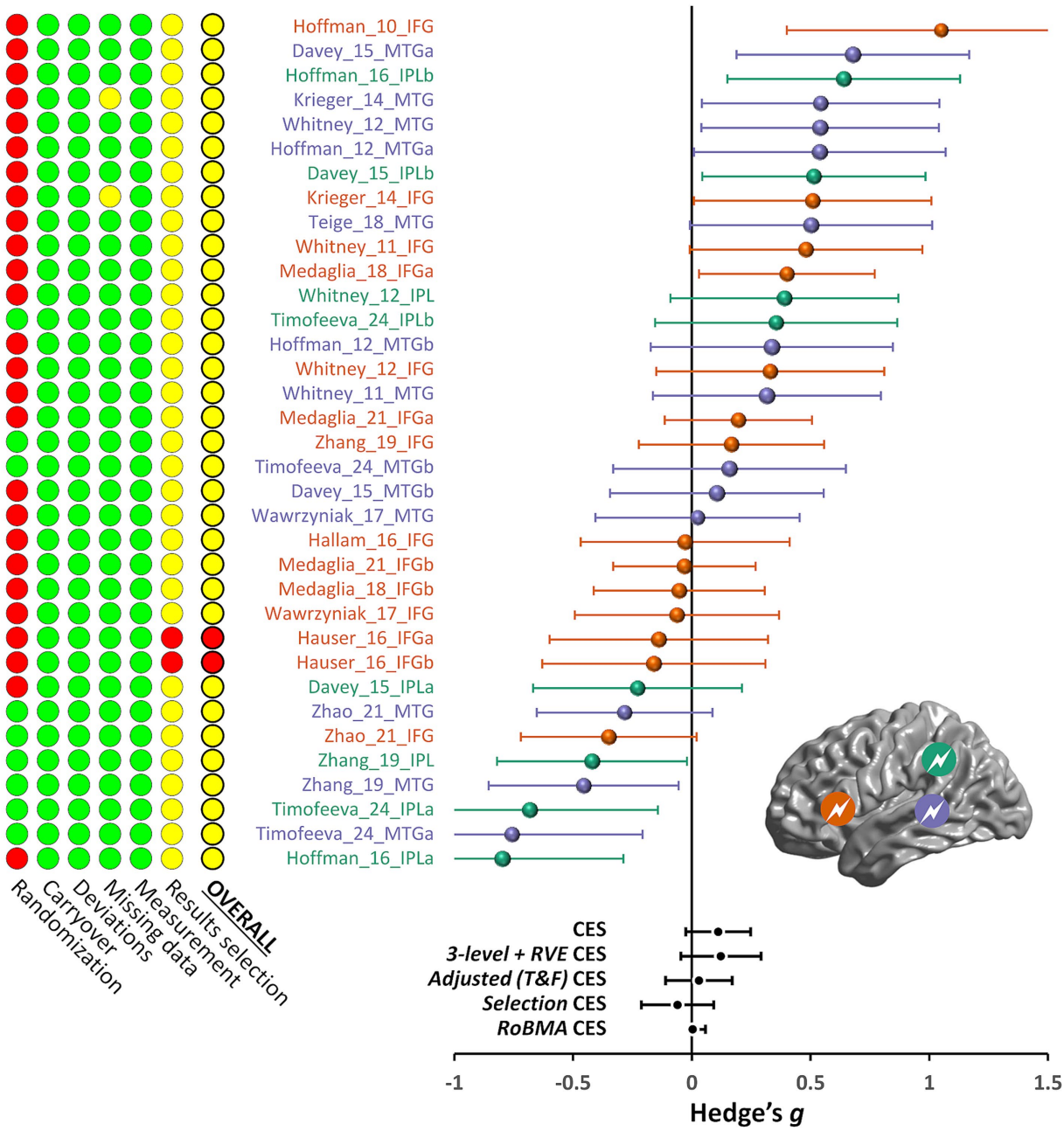

FIGURE 2
Risk of bias and effect sizes for the included effects. The traffic light plot on the left shows the risk of bias summary based on the authors' judgments about each risk of bias item for each included study. Green, yellow, and red indicate low, unclear, and high risk of bias, respectively. See the main text for the description of the risk of bias dimensions. The forest plot on the right summarizes the meta-analysis results for all the included effects. Effects indicated in orange, purple, and green are derived from TMS stimulation of IFG, pMTG, and IPL, respectively (see inset); suffixes *a* and *b* indicate multiple effects from the same study and stimulated region. The bottom part of the forest plot shows the combined effect sizes (CES) derived from different meta-analytical approaches, as described in detail in the main text (*3-level + RVE*, three-level random effects model with a cluster-robust variance estimation method; *T&F*, trim-and-fill; *RoBMA*, robust Bayesian meta-analysis).

from −0.037 to 0.283 [$t(34) = 1.567$, $p = 0.127$; see Figure 2] and substantial heterogeneity among the true effects [$Q(34) = 104.54$, $p < 0.001$]. The results were essentially the same when using the cluster-robust variance estimation ($M = 0.122$, $CI_{95\%} = [-0.046–0.292]$, $t(34) = 1.567$, $p = 0.140$). However, it should be noted that the log-likelihood ratio test revealed that the inclusion of the random level for the studies, to account for effect size dependency, was not justified [$X(1) = 0.786$, $p = 0.375$].

The funnel plot displayed in Figure 3 showed a slight asymmetry of the included effects (filled circles), as confirmed by the rank correlation test (Kendall's $\tau = 0.267$, $p = 0.024$) but not the Egger's regression test ($Z = 1.82$, $p = 0.069$), suggesting that some publication bias might exist. The trim-and-fill method estimated that 5 studies were missing (empty circles). The combined effect size estimate obtained after their inclusion was thus even reduced ($M = 0.03$, $CI_{95\%} = [-0.11–0.17]$; see Figure 2).

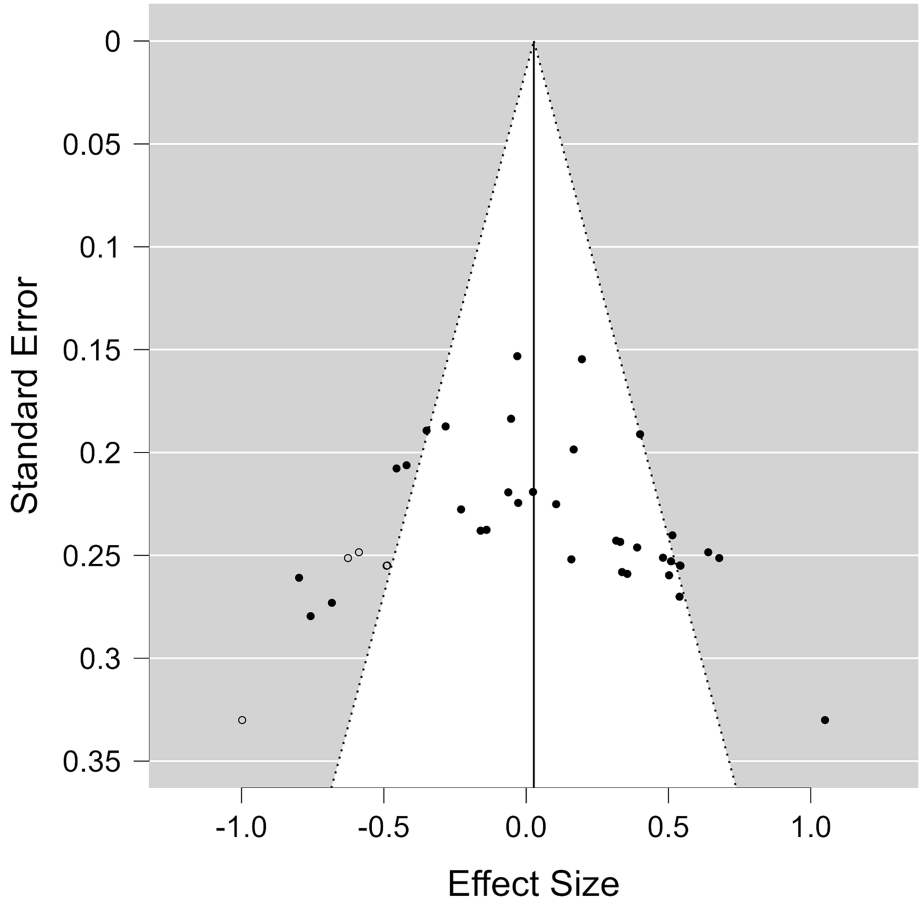

FIGURE 3
Trim-and-fill funnel plot. The funnel plot shows the effect sizes of the individual effects included in the meta-analysis as black dots. The empty dots represent the imputed and added effects after the trim-and-fill analysis.

Regarding the heterogeneity selection models, since the test was significant, we proceeded with a random effect model (Bartoš et al., 2022). The point estimate of the combined effect was very close to that found in the classical meta-analysis, reported above ($M = 0.111$, $CI_{95\%} = [-0.024–0.246]$). However, this analysis also revealed a significant publication bias [$\chi^2(1) = 5.050$, $p = 0.025$], indicating that non-significant results are less likely to be published compared to significant results. Adjusting for this publication bias led to a non-significant and negative effect size estimate ($M = -0.060$, $CI_{95\%} = [-0.213–0.092]$, $z = -0.774$, $p = 0.439$). Adjusted estimated heterogeneity was $\tau = 0.333$ (the unadjusted one was $\tau = 0.228$).

The results of the RoBMA analysis estimated the mean effect of the TMS-dependent change in semantic control performance between the active and control TMS groups/conditions and the corresponding $CI_{95\%}$ displayed in the forest plot in Figure 2. The model-averaged estimated combined effect size was g = 0.004 (median = 0), with a 95% credible interval of [0–0.057]. The analysis found strong evidence for the absence of the investigated effect ($BF_{01} = 12.361$) and strong evidence for the existence of publication bias ($BF_{10} = 103.728$). The best model was that including the publication bias but not the investigated effect and the heterogeneity (BF = 9.115).

Regarding the z-curve analysis (see Figure 4), the conditional power of the significant results was estimated to be very low (ERR = 25%, $CI_{95\%} = [3–76\%]$); in other words, this analysis estimated that exact replication attempts of the included significant results would be expected to succeed 25% of the time. Furthermore, the unconditional power of any potential study was estimated to be even lower (EDR = 7%, $CI_{95\%} = [5–70\%]$), suggesting that only 7% of the studies would find a significant result. Since the observed discovery rate was considerably higher (ODR = 37%, $CI_{95\%} = [22–55\%]$) and its confidence interval did not include the EDR value, the results of this analysis provide statistically significant evidence for the existence of publication bias.

The sensitivity analysis confirmed the results reported above, showing that they were not dependent on our choice of the value for the correlation between repeated measures. Finally, we re-ran all the analyses reported above after excluding the effects related to IPL stimulation, because its inclusion in the multimodal semantic control network revealed by the Noonan and colleagues' meta-analysis (2013) was not confirmed in a more recent meta-analysis (Jackson, 2021). The results reported above were substantially the same, confirming that there was no evidence to support a meaningful average effect and showing the presence of publication bias.

4 Discussion

This quantitative meta-analysis aims to assess the current state of research derived from transcranial magnetic stimulation (TMS) studies that allowed us to assess the predictions of the Controlled

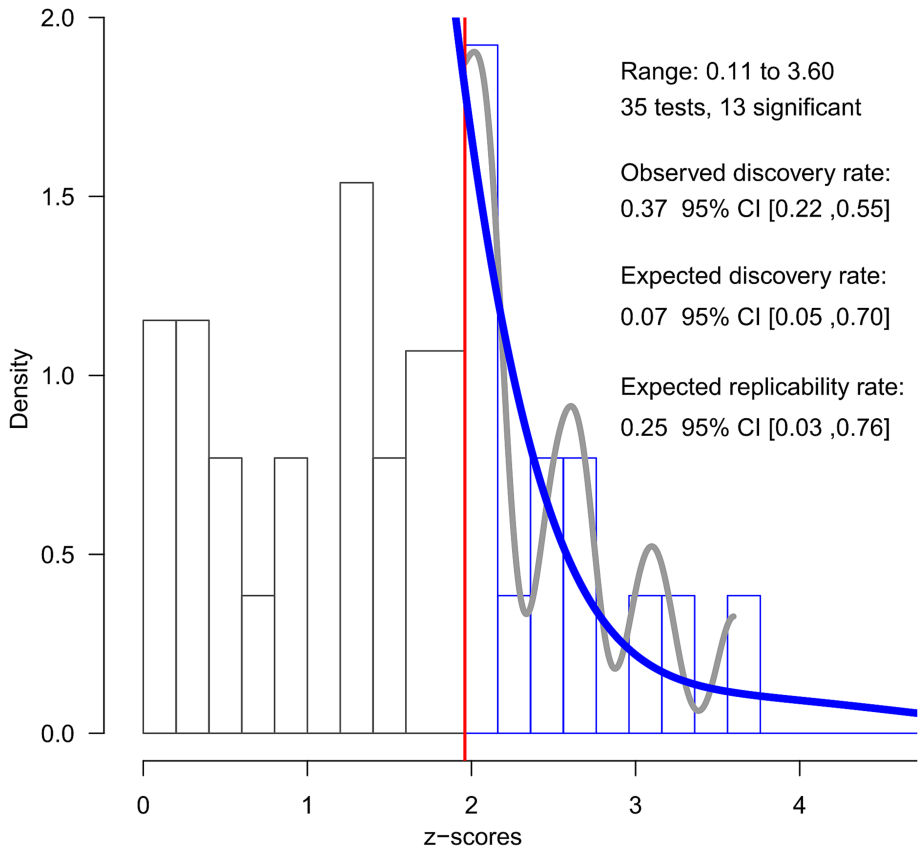

FIGURE 4
Z-curve analysis. The figure shows the results of the *Z*-curve analysis of the included effects converted into *z*-scores. The histogram displays the distribution of observed *z*-scores from the 35 effects included, with 13 being statistically significant ($z > 1.96$, indicated by the red vertical line). The grey line represents the observed density of the significant *z*-scores, while the solid blue line depicts the fitted *z*-curve model.

Semantic Cognition (CSC) framework (Lambon Ralph et al., 2017). Specifically, we examined evidence concerning the role of the inferior frontal gyrus (IFG), posterior middle temporal gyrus (pMTG), and inferior parietal lobule (IPL) in semantic control abilities (Lambon Ralph et al., 2017), as assessed by studies using inhibitory TMS interventions that are assumed to induce a reversible virtual lesion to these brain areas and, thus, to induce temporary semantic control deficits. To achieve this, we first identified all relevant studies published up until August 2024 in international journals ($N = 16$). We then assessed the robustness of their results using various analytical methods. Here, we discuss our primary findings and their implications in detail.

4.1 Robustness of evidence from TMS studies on semantic control abilities

The frequentist analysis revealed a small, non-significant combined effect size of TMS on semantic control processes. This result was accompanied by high variability (heterogeneity) across studies, which suggests that results differ substantially depending on specific experimental setups or conditions. Both these results do not support a consistent role of the three analyzed brain regions in semantic control. Given that many effects were derived from the same articles or laboratories, we performed a three-level random effects model accounting for effect size dependency. This confirmed the lack of significant effects across all three brain regions. These results were also confirmed by a selection model, and a robust Bayesian meta-analysis (RoBMA, Bartoš and Maier, 2020), a method that incorporates uncertainty and prior information, not only confirmed the absence of a significant effect but provided evidence for the absence of such an effect.

As regards publication bias, it was indicated by the slight funnel plot asymmetry in the classical random model, suggesting that approximately five studies with non-significant outcomes might be missing from the published literature. After applying the trim-and-fill procedure, which estimates and adjusts for missing studies, the average effect size was even reduced. We further scrutinized publication bias using a selection model and a *z*-curve analysis, which revealed a potential compromise in the evidential values of TMS effects on semantic control, indicating that significant findings may be overrepresented due to publication bias. Finally, the RoBMA analysis provided strong statistical evidence for the existence of publication bias, highlighting the need for caution in interpreting positive results.

These findings do not necessarily disprove the authors' theoretical claims or suggest intentional misconduct. However, they highlight potential methodological issues, such as the adequacy of analysis and reporting. Therefore, readers should critically evaluate the reported successes. Still, these results seem to not support the contributions of

the IPL, IFG and pMTG to semantic control processes as proposed by the CSC framework (Lambon Ralph et al., 2017) and evidenced by the Noonan and colleagues' meta-analysis of fMRI findings (2013). This conclusion of a lack of involvement of these brain regions in semantic control processes is thus puzzling, especially for IFG and pMTG. Indeed, the contribution of these regions to semantic control has been confirmed in a number of neuroimaging studies and in a recent fMRI meta-analysis (Jackson, 2021), which, however, did not find an effect for IPL. This might be due to the fact that different parts of IPL have different roles in semantic cognition. For example, ventral angular gyrus is typically implicated in easier rather than harder tasks, suggesting a role in semantic representation rather than in semantic control. It seems that only the dorsal part of the angular gyrus and intraparietal sulcus has a domain-general control role (Fedorenko et al., 2013), a role that would probably fail to show up when participants' performance in a semantic control task is compared with a general control task. It should also be noted that studies targeting IPL were fewer in number and they targeted IPL in both the hemispheres. This could have decreased the effect size for IPL since the effect is supposed to be stronger in the left hemisphere according to the CSC framework. Still, our findings were confirmed even after excluding IPL outcomes, suggesting that their inclusion did not bias our conclusions.

A more straightforward interpretation of our findings is that the inhibitory TMS stimulation applied in the included studies over these areas was not effective in impairing participants' performance under high semantic control demands. Indeed, while our results show no significant effects of TMS, the methodological variability in the experimental designs across studies may have further reduced the likelihood of detecting consistent effects. Moreover, evidence of publication bias suggests that non-significant results may be underrepresented in the literature. These findings raise questions about the reliability of TMS in simulating deficits in semantic control and highlight the need for methodological improvements in future studies.

4.2 Methodological strengths and limitations of the TMS studies

Some key aspects of the methodological soundness and homogeneity of the selected TMS studies should be highlighted because they contribute to strengthening the conclusions of the meta-analysis. To begin with, it is imperative to acknowledge that most of these studies employed an offline inhibitory TMS (13 out of 16 studies), facilitating cross-study comparisons. Second, all studies employed individualized structural imaging guidance that increases the efficacy of locating stimulation sites over scalp-based targeting methods (Beynel et al., 2019; Sack et al., 2009). This method considers interindividual differences in brain anatomy and is more accurate for fine-grained targeting. Reliable identification of the sites is the first step in a successful understanding of the neural substrate underlying the process of interest. Another consistent and positive aspect in all analyzed studies was the amplitude dosing of the TMS stimulation based on the motor threshold of the participants (13 out of 16 studies). Although this may be inappropriate to guide amplitude stimulation in non-motor areas of the brain, it still considers individual differences in the physiological response induced by stimulation. Finally, to ensure that the observed results could not be explained by the nonspecific effects of the TMS procedure or the general difficulty of the task, eleven studies included a control task, such as a number judgment (Hoffman et al., 2010; Zhang et al., 2019), number naming (Medaglia et al., 2018, 2021) and Navon (Whitney et al., 2011, 2012) tasks. The use of a control task offers significant advantages by elucidating the precise role of a specific brain region. Indeed, this methodology proves to be more insightful, as it enables a direct comparison between the effects of TMS on the experimental task of interest and the control task. The expectation here was that TMS should manifest an impact on the target task, which involves the semantic control process, while leaving the control task relatively unaffected (e.g., the number judgment task).

However, we point out that most of these studies were short in power as they used fairly small sample sizes, as supported by the *z*-curve analysis. This limitation is exacerbated by the employment of the same participants under multiple conditions and experiments in some studies. These shortcomings could increase the risk of finding false negatives and inflated effect sizes (Button et al., 2013; Ioannidis, 2005), ultimately undermining result reliability and replicability.

The risk of bias in selecting the results reported in most TMS studies has also emerged. However, it should be noted that this factor raises 'some concerns' in a study even only if the data analysis plan is not pre-registered. The practice of pre-registration, which was notably infrequent during the era in which several of these studies were undertaken, has emerged in recent years as an increasingly esteemed methodology within the realm of research. This paradigm shift toward pre-registration can be attributed to its manifold advantages, foremost among them being the safeguard against the common pitfall of researchers tailoring their results to fit the data, thus mitigating the risk of overfitting. Additionally, it serves as a powerful instrument in augmenting the transparency and methodological rigor of research endeavors, thereby fortifying the foundations upon which scientific conclusions are built. Furthermore, pre-registration provides a unique opportunity to meticulously scrutinize *a priori* theories, affording scholars a means to assess hypotheses empirically and comprehensively before the onset of data collection, fostering a more robust scientific discourse.

Randomization and allocation concealment, critical to reducing bias, were generally not feasible in TMS studies., In TMS studies, participants and, especially, experimenters are likely aware of the type of stimulation being administered. Indeed, participants can often distinguish between real stimulation, which induces a stronger physical sensation at the stimulation site, and sham stimulation. Additionally, experimenters always know the condition (e.g., site and type of TMS stimulation) they are administering.

Another methodological issue in TMS studies is the inconsistent settings and adjustment for participants discomfort that may have reduced the comparability and efficacy of stimulation across studies. For example, in our meta-analysis, 13 out of 16 studies used stimulation intensities ranging from 80 to 120% of the active or resting individual motor threshold, while three studies used fixed stimulation intensities for all participants. In both cases, it remains unclear if these measures are the most reliable for stimulating areas outside the motor cortex. Furthermore, in some studies, the stimulation intensity was reduced due to participants experiencing pain sensations (Häuser et al., 2016; Whitney et al., 2011, 2012).

4.3 Methodological recommendations

Recent practices and recommendations for psychological studies could also be adopted in this specific field without compromising methodological rigor. As previously mentioned, most TMS studies on semantic control are severely underpowered due to relatively small sample sizes, with a few exceptions (Zhang et al., 2019; Medaglia et al., 2018, 2021). It is worth noting that Medaglia et al.'s studies used a between-subject design, which is known to be less powerful than a within-subject design. All the included studies had sample sizes smaller than 20, which is associated with low statistical power. This lower power increases the likelihood of false negatives and overestimation of true effect sizes (Button et al., 2013; Ioannidis, 2005). Larger sample sizes are crucial for obtaining reliable and valid results. Small samples are also more susceptible to the researcher's degrees of freedom (e.g., trying several procedures of outlier exclusion and data analyses, etc.), which increases the probability of obtaining significant results by chance (Simmons et al., 2011).

A third way to potentially improve research on semantics methodologically, and consequently enhance our understanding of semantic control, is to preregister the study hypothesis, sample size, and analysis plan in repositories like Open Science Framework[2] and Protocols.io[3] before starting the experiment (for details, see Simmons et al., 2021). Researchers should also consider publishing their studies as registered reports (i.e., articles accepted before data collection and analysis, provided they meet required quality standards) (Chambers and Tzavella, 2022). This approach will facilitate the dissemination of negative and null results and prevent p-hacking and HARKing (Simmons et al., 2021) thereby reducing risks associated with publication bias.

Finally, we observed that most of the selected studies (e.g., Whitney et al., 2011, Krieger-Redwood and Jefferies, 2014; Hallam et al., 2016) used analyses of variance. However, in psycholinguistic and neurolinguistic research, participants are often presented with lists of linguistic stimuli, and researchers aim to draw general conclusions that extend beyond the specific sample and the set of items used. Linear mixed-effects modeling would be a more appropriate approach for analyzing this type of data, offering several advantages over traditional general linear model analyses (such as repeated measures analysis of variance and multiple regression). Unlike general linear models, mixed-effects models do not require prior averaging across participants and items, thus preserving and considering their variability (Montefinese et al., 2014; Visalli et al., 2023; Viviani et al., 2024). This approach increases the accuracy and generalizability of parameter estimates, allowing for a better evaluation of the effects of predictors (i.e., variables of interest and confounding factors, such as word frequency and length) and providing stronger protection against capitalization on chance, or Type I error (Baayen et al., 2008; Quené and van den Bergh, 2008). Therefore, a final recommendation for future neurostimulation studies on semantic control processes is to adopt linear mixed-effects models as a standard practice in their analysis routine, as it will enhance the credibility of their outcomes.

2 https://www.cos.io/initiatives/prereg

3 https://www.protocols.io/

5 Conclusion

In this meta-analysis, we examined TMS studies targeting the IFG, pMTG, and IPL to assess their role in semantic control. Our results seem to challenge the contributions of IFG and pMTG to semantic control processes as proposed by the CSC framework (Lambon Ralph et al., 2017) and the fMRI meta-analysis by Noonan et al. (2013). This is puzzling, given the strong evidence from fMRI studies for these regions' roles in semantic control. However, our findings may reflect limitations in TMS methodology rather than an actual absence of functional contributions by these regions. One plausible explanation for the lack of significant findings is that the inhibitory TMS protocols used in these studies may not have effectively disrupted participants' performance on tasks requiring high semantic control. Methodological variability—such as differences in task design and stimulation protocols—might have limited the reliability of TMS in simulating deficits in these processes and raises concerns about the replicability of the observed effects. Furthermore, our study revealed stronger evidence for the existence of publication bias, raising questions about whether the literature represents the full scope of TMS outcomes. Future studies should adopt more rigorous methodologies, including larger sample sizes, pre-registration of study designs, and advanced statistical techniques to enhance the reliability of TMS as a tool for investigating the neural mechanisms underlying semantic control.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the data for the meta-analysis have been derived from previously published studies. Requests to access these datasets should be directed to Maria Montefinese, maria.montefinese@unipd.it.

Author contributions

EA: Data curation, Formal analysis, Funding acquisition, Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. SB-V: Writing – original draft, Writing – review & editing. AV: Writing – review & editing. GV: Writing – review & editing. MM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Resources, Software, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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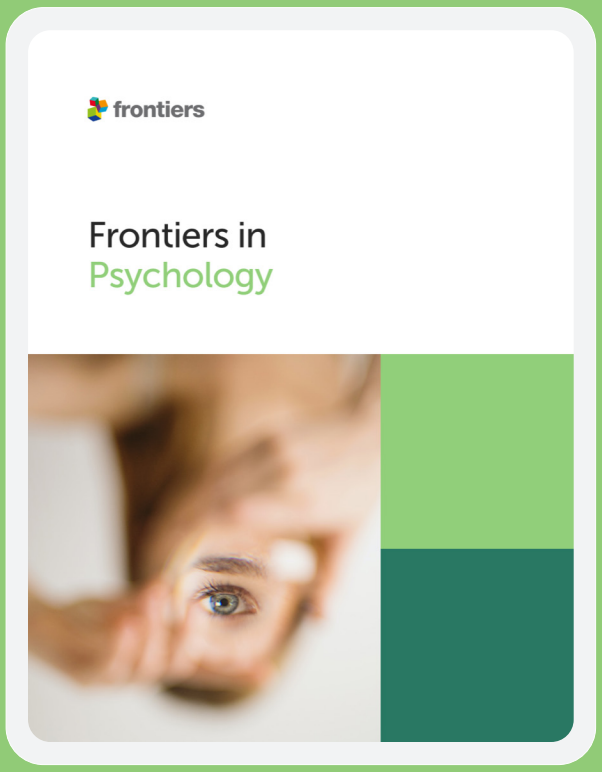

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