



cTBS to Right DLPFC Modulates Physiological Correlates of Conflict Processing: Evidence from a Stroop task

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Abstract

Conflict typically occurs when goal-directed processing competes with more automatic responses. Though previous studies have highlighted the importance of the right dorsolateral prefrontal cortex (rDLPFC) in conflict processing, its causal role remains unclear. In the current study, the behavioral experiment, the continuous theta burst stimulation (cTBS), and the electroencephalography (EEG) were combined to explore the effects of behavioral performance and physiological correlates during conflict processing, after the cTBS over the rDLPFC and vertex (the control condition). Twenty-six healthy participants performed the Stroop task which included congruent and incongruent trials. Although the cTBS did not induce significant changes in the behavioral performance, the cTBS over the rDLPFC reduced the Stroop effects of conflict monitoring-related frontal-central N2 component and theta oscillation, and conflict resolution-related parieto-occipital alpha oscillation, compared to the vertex stimulation. Moreover, a significant hemispheric difference in alpha oscillation was exploratively observed after the cTBS over the rDLPFC. Interestingly, we found the rDLPFC stimulation resulted in significantly reduced Stroop effects of theta and gamma oscillation after response, which may reflect the adjustment of cognitive control for the next trial. In conclusion, our study not only demonstrated the critical involvement of the rDLPFC in conflict monitoring, conflict resolution processing, and conflict adaptation but also revealed the electrophysiological mechanism of conflict processing mediated by the rDLPFC.

Keywords Conflict Processing · The Right DLPFC · N2 · Neural Oscillation · cTBS

Introduction

Conflict typically occurs when goal-directed processing competes with more automatic responses. The Stroop task, as one of the most well-established paradigms in cognitive neuroscience, has been frequently used to investigate conflict-related processing (MacLeod 1991; Stroop 1935). In the classic color-word Stroop task, subjects are asked to report the ink color of the presented color words (Stroop

1935). Of these words, some of them were incongruent, such as “RED” printed in green font, and the others were congruent, where the color name was printed in the same color as the word meaning (e.g., “RED” printed in red font). The cognitive model assumes that word meanings are processed automatically (MacLeod 1991), so incongruent stimuli result in slower response times (RTs) compared to congruent ones. The result of incongruent trials minus congruent trials was known as the Stroop effect (Friebs et al. 2020; Frings et al. 2018).

Multiple neuroimaging studies based on functional magnetic resonance imaging (fMRI) have found greater activity of the DLPFC for the incongruent trials than for the congruent trials, highlighting the important role of the dorsolateral prefrontal cortex (DLPFC) in conflict processing (Hinault et al. 2019; Noah et al. 2017; Parris et al. 2019; Wang et al. 2021; Wittfoth et al. 2009). The classical conflict monitoring theory suggests that the anterior cingulate cortex monitors conflict and then triggers the DLPFC to regulate and resolve the conflicts (Botvinick et al. 2004; Carter and van Veen

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2007). However, a study employing a Simon task found concurrent activation of the DLPFC in three distinct conflict-related conditions, indicating the involvement of the DLPFC in conflict monitoring (Wittfoth et al. 2009). Therefore, the role of the DLPFC in conflict monitoring is somewhat controversial. Notably, these studies have emphasized the association between the DLPFC and conflict processing, but they have not established a causal relationship.

Transcranial magnetic stimulation (TMS) has been utilized to explore the functional relevance of the DLPFC on conflict processing (Anderkova et al. 2018; Friehs et al. 2020; Muhle-Karbe et al. 2018). TMS generates a strong magnetic field around a coil, inducing a current in the underlying neuronal tissue. The continuous theta burst stimulation (cTBS), a well-established repetitive TMS (rTMS) protocol, can modulate neural excitability (Huang et al. 2005), especially the prefrontal cortex (Ngetich et al. 2021). Numerous TMS studies using the Stroop task have explored the relationship between the left DLPFC and conflict processing from a behavioral perspective (Friehs et al. 2020; Kim et al. 2012; Muhle-Karbe et al. 2018; Parris et al. 2021; Vanderhasselt et al. 2006), demonstrating the causal role of the left DLPFC in conflict processing (Kim et al. 2012; Yu et al. 2022). For instance, a study applying the high-frequency rTMS to the left DLPFC found improved reaction time in incongruent trials after the rTMS stimulation than before the stimulation (Kim et al. 2012). Another study showed that high-frequency rTMS over the left DLPFC in patients with executive dysfunction after stroke significantly reduced the Stroop effect in response time compared to sham stimulation (Yu et al. 2022). However, the causal role of the right DLPFC (rDLPFC) in conflict processing remains ambiguous, with only a few studies exploring it (Anderkova et al. 2018; Friehs et al. 2020; Zack et al. 2016). An early study found that the cTBS applied to the rDLPFC increased the Stroop effect of RT for men with pathological gambling (Zack et al. 2016), indicating a potential influence of the rDLPFC activity on conflict resolution. More recent studies found no moderating effect of the TMS over the rDLPFC on the Stroop effect for healthy participants (Anderkova et al. 2018; Friehs et al. 2020), which did not support a causal role for rDLPFC in conflict resolution. To further investigate these controversies, the current study focused on exploring the causal role of the rDLPFC in conflict processing.

Changes in neural activity induced by cTBS can be measured by electroencephalography (EEG). Indeed, the TBS-EEG has been employed to reveal neural mechanisms mediating cognitive neuroscience, such as language switching (Pestalozzi et al. 2020), working memory (Chung et al. 2019), and pain-related information integration (Che et al. 2019). Previous human EEG studies have identified three main components associated with conflict processing with

the Stroop task: the N2 component, theta oscillation, and alpha oscillation. The frontal-central N2 component has a larger amplitude in the incongruent stimuli than the congruent stimuli or the neutral stimuli (Boenke et al. 2009; Donohue et al. 2016; Grutzmann et al. 2014; Xu et al. 2023). Its generator has been localized within the DLPFC and the anterior cingulate cortex (Bocquillon et al. 2015). Moreover, the strength of the N2 component is positively related to the performance of the Stroop task (Overbye et al. 2021), suggesting its involvement in conflict monitoring and cognitive control (Heidlmayr et al. 2020; Larson et al. 2014). Additionally, multiple studies have found stronger frontal-central theta oscillations in incongruent stimuli compared to neutral or congruent stimuli, indicating conflict monitoring (Eschmann et al. 2018; Fusco et al. 2022; Hacıahmet et al. 2023; Hanslmayr et al. 2008; Itthipuripat et al. 2019; Naylor et al. 2012; Zhao et al. 2015). The intracranial EEG recordings in patients with medically refractory epilepsy have further demonstrated increased theta power localized to the bilateral DLPFC during conflict processing, highlighting the association between DLPFC and theta oscillations (Bartoli et al. 2018). In addition, the parieto-occipital alpha oscillations are commonly associated with conflict resolution (Ergen et al. 2014; Gu et al. 2019; Jiang et al. 2015), reflecting inhibitory control for the motor response tendencies during conflict resolution (Ergen et al. 2014). Several studies have reported a significant reduction in alpha oscillations during incongruent trials compared to congruent trials (Chen et al. 2022; Ergen et al. 2014; Gu et al. 2019; Jiang et al. 2015).

Overall, based on the Stroop task, the current TMS studies explore the causal role of the rDLPFC in conflict processing from a behavioral perspective, which is to some extent controversial. In addition, the impact of the rDLPFC stimulation on the physiological correlates associated with conflict processing in the Stroop task remains unknown. The current study applied the cTBS over the rDLPFC and used the EEG to record the signal based on the color-word Stroop task, to further explore the causal role of the rDLPFC in conflict processing. We hypothesize that the cTBS over the rDLPFC will affect the behavioral performance. Additionally, previous fMRI studies have highlighted the importance of the DLPFC in conflict monitoring and conflict resolution, while EEG studies have identified conflict monitoring-related N2 components and theta oscillations, as well as conflict resolution-related alpha oscillations. Therefore, we also hypothesize that modulation of the rDLPFC activity through cTBS will impact these physiological correlates associated with conflict processing.

Materials and Methods

Participants

Twenty-six healthy right-handed students from the University of Electronic Science and Technology of China (UESTC) were recruited for the study. The sample size for the study was determined using G*Power 3.1.9.7 software (Heinrich Heine University in Dusseldorf, Germany). The a priori sample size calculation was based on the α error prob of 0.05, the power ($1-\beta$ error prob) of 0.95, and the effect size ($f=0.25$), and it resulted in a calculated sample size of eighteen participants. All participants were native Chinese speakers with normal or corrected-to-normal vision, who had no prior neurological, psychiatric, or cardiovascular disease. The study was approved by the UESTC Ethics Committee, and conducted in accordance with the approved guidelines and the Declaration of Helsinki. We obtained written informed consent from all participants before the experiment and gave them monetary compensation at the end of the experiment. All the participants were unaware of the stimulation site and the consequences. We excluded two participants from subsequent analyses due to data loss during data collection, resulting in a total of twenty-four subjects (12 women, mean age = 22 ± 2.23 SD years, range: 18–27 years).

Experimental Design and Procedure

The experiment was conducted using a single-blind design, ensuring that all participants remained unaware of both the stimulation site and the potential consequences of the experiment. Participants underwent two experimental sessions that varied in the TMS site (the right DLPFC vs. vertex), each seven days apart to prevent any potential carry-over effects (Che et al. 2019; Lowe et al. 2018). The order of sessions was counterbalanced among participants to the best possible degree. Our design yielded two possible

stimulation sequences, each planned to recruit twelve participants. Due to complications during data collection, one sequence was completed by eleven participants, while the other by thirteen participants. In each session, the resting-state EEG data were first collected for two minutes in the eyes-open (EC) and eyes-closed (EO) states, respectively. A Stroop task was then performed along with EEG data recording. Next, the cTBS protocol was applied to the TMS site. After a three-minute break, the EEG data for the EC state were collected for two minutes, followed by the Stroop task. In other words, about a five-minute break was included before the Stroop task (Che et al. 2019; Ngetich et al. 2021). Finally, the EEG data for the EO state were collected for two minutes. The details are shown in Fig. 1A.

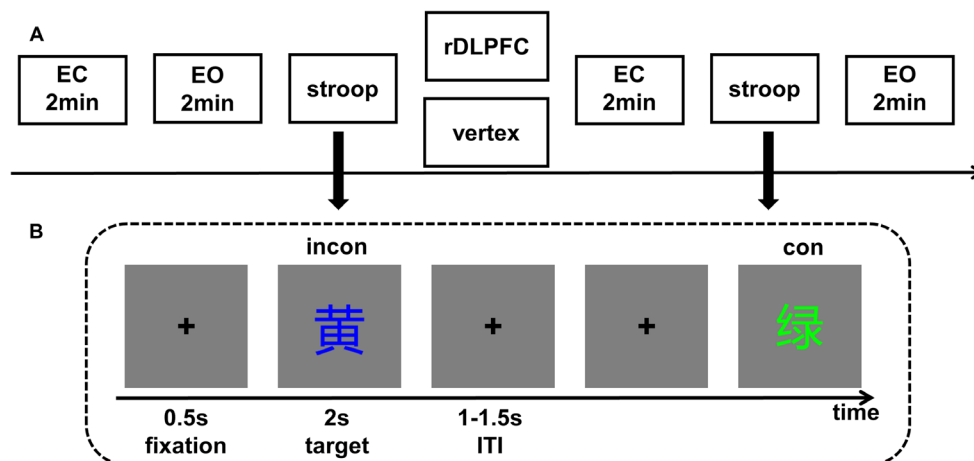
Stimuli and Task

The stimuli consisted of four words (“RED”, “YELLOW”, “BLUE”, and “GREEN” in Chinese characters), which were presented using the Microsoft Yahei font (font size 60) on a gray background (RGB values 127, 127, 127). The stimuli were presented either in red (RGB values 255, 0, 0), green (RGB values 0, 128, 0), blue (RGB values 0, 0, 255), or yellow (RGB values 255, 255, 0). The print colors were randomly matched to the words, resulting in sixteen different color-word stimuli. The print color and word meaning corresponded in the congruent trials, whereas they did not in the incongruent ones.

Each trial started with a central fixation for 0.5ms, followed by the color-word stimulus that was presented for 2ms. Subjects were asked to press either key ‘f’ or key ‘j’ on the keyboard with the index finger of their left and right hands as quickly as possible, reporting whether the stimulus was congruent or incongruent. The central fixation was then presented for 1–1.5ms randomly. An example of the paradigm can be seen in Fig. 1B.

Four experimental blocks were involved in the Stroop task, with each having thirty-six congruent and thirty-six

Fig. 1 A: The experimental procedure. B: An example of the Stroop task. EC: eyes-closed state. EO: eyes-open state. cTBS: continuous theta burst stimulation. rDLPFC: the right dorso-lateral prefrontal cortex. Min: minutes. ITI: intertrial interval



incongruent trials, resulting in a total of 144 congruent trials and 144 incongruent trials for each participant. The congruent trials contained four kinds of stimuli (i.e., where red /green /blue/yellow was printed as red/green/blue/yellow), with each stimulus comprising thirty-six trials. The twelve different word x printed color stimuli were contained in incongruent trials, with each stimulus comprising twelve trials. Additionally, the congruent and incongruent trials were not repeated over four consecutive trials to avoid any possible potential contingency learning effect (Hasshim and Parris 2021; Jacoby et al. 2003), and all trials were presented in pseudo-random order. Before each session, subjects were required to do the practice block with twelve congruent and twelve incongruent trials. All the tasks are implemented through E-Prime 3.0 (Psychology Software Tools, Pittsburgh, PA, United States).

Transcranial Magnetic Stimulation

In the current study, the cTBS consisted of a burst of 3 pulses given at 50 Hz and repeated every 5 Hz to yield a total of 600 pulses (Huang et al. 2005), which were delivered over the EEG cap using a Magstim super rapid magnetic stimulator with a figure-of-eight coil (diameter 70 mm) (Magstim Company Limited, Whiteland, United Kingdom). The cTBS protocol was performed using the Montreal Neurological Institute (MNI) coordinate for the right DLPFC ($x=44$, $y=10$, $z=30$), which was obtained from two meta-analysis studies that explored activated brain regions associated with the Stroop effect in the color-word Stroop task (Cieslik et al. 2015; Xu et al. 2016). To target the individual stimulation site, the high-resolution anatomical T1-weighted MRIs were acquired with a 3.0 T GE Sigma scanner for all participants before the experiment with the following parameters: TR=5.96 ms, TE=1.96 ms, flip angle=9°, FOV=256×256 mm², matrix size=256×256, voxel size=1×1×1 mm³, 176 slices. The participant's brain was co-registered to the TMS coil using the anatomical information imported into the BrainSight stereotaxic neuronavigation system (Rogue Research, Montreal, Quebec, Canada). The vertex was selected as the control site with the MNI coordinate ($x=0$, $y=0$, $z=90$). The TMS coil was oriented at 45° to the sagittal plane and more than 10 cm from the vertex site to provide the same sound but not interfere with ongoing task-related activities. The stimulation intensity was set to 50% intensity of the TMS maximum stimulator output and was finely adjusted according to the subjects' tolerance. Almost all subjects were able to tolerate this stimulation intensity, excluding one subject (45% of the TMS maximum stimulator output). Overall, all TMS pulses were applied within recommended safety limits (Keuper et al. 2018; Rossi et al. 2009; Viejo-Sobera et al.

2017). Participants were asked to avoid movements during the stimulation period, and all of them could tolerate this procedure.

EEG Recording

The eego™ mylab system (ANT Neuro b.v., Hengelo, the Netherlands) with a 64-channel waveguard™ EEG cap was used to collect the continuous EEG data. Horizontal electrooculograms (EOGs) were obtained from one electrode located at the outer canthus of the left eye. The sampling rate was set to 1000 Hz, and the impedances were kept below 10 kΩ throughout the experiment (Keuper et al. 2018). The GND and CPz were used as the ground and reference electrodes, respectively.

ERP Analysis

EEG data were preprocessed offline using custom-written scripts that implement functions from the EEGLAB toolbox (version 13.6.5b). A hamming windowed FIR filter (band-pass: 0.1–30 Hz) was first applied to the continuous EEG data. The EEG data were then segmented into epochs (from –200 to 800 ms relative to the onset of the target display). Next, error trials, trials following an error, and the first trial of each block were excluded to avoid any effect related to the error response or contingency learning. Subsequently, the EEG data were re-referenced against the average of all channels and baseline-corrected for 200 ms before the stimulus display. Afterward, channels with an amplitude exceeding 100 μV were marked as bad and replaced via the superfast spherical interpolation, less than five channels were replaced for each condition across all participants. Additionally, trials with EEG activity greater than 100 μV were excluded from the analysis (Yang et al. 2017), and more than 120 trials remained for each condition across all participants. Finally, to remove the artifacts such as blinks and lateral eye movements, we applied the independent component analysis (ICA) (EEGLAB toolbox).

The average ERP waveforms and the topographic maps demonstrated the frontal-central N2 component. The N2 component was defined as the largest negative deflection in the 250–320ms time window relative to the target onset (Heidlmayr et al. 2020). The peak amplitudes and latencies of the N2 component were measured and averaged across the frontal-central electrodes (Fz, FCz, C1, Cz, C2) (Boenke et al. 2009).

Time-frequency Analysis

The preprocessing steps were the same as the ERP analysis, except for the following parameters. A 48 Hz low-pass

filter was applied, with the time epochs ranging from -1500 to 2000 ms relative to the onset of the target. Considering the long time epochs, the channel replacement criteria were set to $\pm 120\mu\text{V}$, leading to less than seven channels being replaced for each condition for each participant. For each participant, more than 130 trials remained for each condition based on the trial rejection criteria ($\pm 150\mu\text{V}$). To obtain the EEG data with better quality, the blind source separation (BSS) algorithm (EEGLAB toolbox) was additionally applied to reject the EOG artifacts before the re-reference.

The time-frequency analysis was then performed using the FieldTrip toolbox (Donders Institute for Brain, Cognition, and Behavior, Nijmegen, Netherlands) and our MATLAB scripts. Continuous wavelet transforms with complex Morlet basis functions were applied. The Morlet wavelet with three cycles was used for 0.5 – 15 Hz in steps of 0.25 Hz and the Morlet wavelet with seven cycles was used for 15 – 45 Hz in steps of 0.5 Hz. To minimize edge effects, we discarded the first 500 ms and the last 500 ms of the time-frequency data after wavelet convolution. The time-frequency data were normalized using the decibel transformation with a period of -500 to -200 ms relative to the target onset.

Previous studies reported that theta oscillation and alpha oscillation were included in the Stroop task (Ergen et al. 2014; Hanslmayr et al. 2008). In the current study, theta oscillation (4 – 7 Hz) and alpha oscillation (8 – 12 Hz) were used for the hypothesis-driven analysis. The topographic maps demonstrated a time window of 90 – 150 ms for the theta oscillation and a time window of 500 – 700 ms for the alpha oscillation. The theta oscillations were averaged across the frontal-central electrodes (FC1, FC2, FCz, C1, Cz, C2), while the alpha oscillations were averaged over the left posterior-occipital electrodes (P3, P5, P7, PO3, PO5, PO7, O1). Additionally, the topographic maps showed significant differences between the left and right hemispheres for alpha oscillations. Hence, an exploratory analysis of the hemispheric differences was performed. The right alpha oscillations were averaged from the electrodes (P4, P6, P8, PO4, PO6, PO8, O2), which were spatially relative to the left hemisphere. To further explore the oscillations that could be modulated by the cTBS over the rDLPFC, cluster-based permutation tests were additionally applied to define the time-frequency regions of interest (TF-ROIs) for the data-driven analysis.

For the data-driven oscillation analysis, cluster-based permutation tests were used for statistical analyses, which provide a straightforward way to solve the problem of multiple comparisons across space (EEG channels) and time (Maris and Oostenveld 2007). To explore the TF-ROIs modulated by the cTBS in the current study, a 2(Type)-by-2(Site) factorial design was applied to test the interactions for the post_cTBS. To further explore the TF-ROIs where

the Stroop effect was directly modulated by the cTBS, another 2 (Time)-by-2 (Site) factorial design was used on the Stroop effects. For both two designs, statistics were performed on each frequency bin. Paired sample t-tests were used across conditions. All adjacent data points exceeding a preset significance level (0.05) were grouped into clusters. We performed 1000 permutations of the random assignment of conditions within subjects, controlling for multiple comparisons ($P < 0.025$; two-tailed test) (Popov et al. 2019; Zhao et al. 2015). The time-frequency pixels including more than 100 consecutive significant time points (100 ms) were retained for each frequency bin. The channels that were co-activated by the time-frequency pixels were then included. After determining the TF-ROIs, grand-average time-frequency representations were separately computed for the congruent and incongruent conditions.

Statistical Analysis

Statistical analyses were conducted using SPSS version 19 (IBM, Somers, NY, USA). Firstly, a three-way repeated measures analysis of variances (ANOVAs) was performed using a 2 (Time: pre_cTBS vs. post_cTBS) $\times$ 2 (Type: incongruent vs. congruent) $\times$ 2 (Site: rDLPFC vs. vertex) design. Then, to investigate the modulatory effect of cTBS on the Stroop effect, the Stroop effect was calculated by subtracting the incongruent trials from the congruent trials, and the two-way 2 (Time) $\times$ 2 (Site) ANOVAs were applied. Greenhouse-Geisser corrections were applied where necessary, and significant interactions were further analyzed using paired sample t-tests. All results were Bonferroni corrected.

For the hemispheric differences in alpha oscillation, the Stroop effect was first calculated, and a three-way ANOVA was performed using a 2 (Time) $\times$ 2 (Site) $\times$ 2 (Hemi: right vs. left) design. The hemispheric differences (right-left) were subsequently calculated and then submitted to the two-way 2 (Time) $\times$ 2 (Site) ANOVAs to explore the modulatory effect of cTBS on the hemispheric difference of alpha oscillation. Pearson's correlations were used to assess the relationships between behavioral performance and all the conflict-related physiological correlates on the Stroop effect, as well as to assess the relationship between the N2 component and the conflict-related oscillations.

Results

Behavioral Results

For the RTs, the three-way 2 (Time) $\times$ 2 (Type) $\times$ 2 (Site) ANOVAs showed a main effect of Time ($F_{(1, 23)} = 9.773$, $p = 0.005$, $\eta_p^2 = 0.298$) and a main effect of Type ($F_{(1, 23)} =$

5.091, $p < 0.001$, $\eta_p^2 = 0.705$). Furthermore, an interaction between Time and Type ($F_{(1, 23)} = 5.844$, $p = 0.024$, $\eta_p^2 = 0.203$) was found.

Subsequent post hoc t-tests found significantly slower RTs for incongruent trials than congruent trials before the vertex stimulation ($t(23) = -8.066$, $p < 0.001$) and before the rDLPFC stimulation ($t(23) = -6.196$, $p < 0.001$), and after the cTBS over the vertex ($t(23) = -4.725$, $p < 0.001$) and the rDLPFC ($t(23) = -5.143$, $p < 0.001$). Furthermore, the rDLPFC stimulation resulted in faster RTs for congruent trials than before the stimulation ($t(23) = 2.891$, $p = 0.048$). Then, the Stroop effect of RT was calculated and submitted to the 2 (Time) $\times$ 2 (Site) ANOVAs. The results revealed a significant main effect of Time ($F_{(1, 23)} = 5.844$, $p = 0.024$, $\eta_p^2 = 0.203$), indicating a reduction in the Stroop effect following the stimulation. For accuracy, a significant main effect of Type was observed in the three-way ANOVAs ($F_{(1, 23)} = 5.375$, $p = 0.030$, $\eta_p^2 = 0.189$), indicating the higher accuracies in incongruent trials than congruent trials, as shown in Fig. 2C–D.

ERP Results

Figure 3 A illustrates the topographies of the frontal-central N2 component (250–320ms). The average waveforms for each condition are shown in Fig. 3B. For the N2 peak amplitude, the three-way 2 (Time) $\times$ 2 (Type) $\times$ 2 (Site) ANOVAs found an interaction between Type and Site ($F_{(1, 23)} = 6.359$, $p = 0.019$, $\eta_p^2 = 0.217$), with smaller N2 amplitude in the incongruent trials than congruent trials after the rDLPFC stimulation ($t(23) = -2.331$, $p = 0.029$), indicating

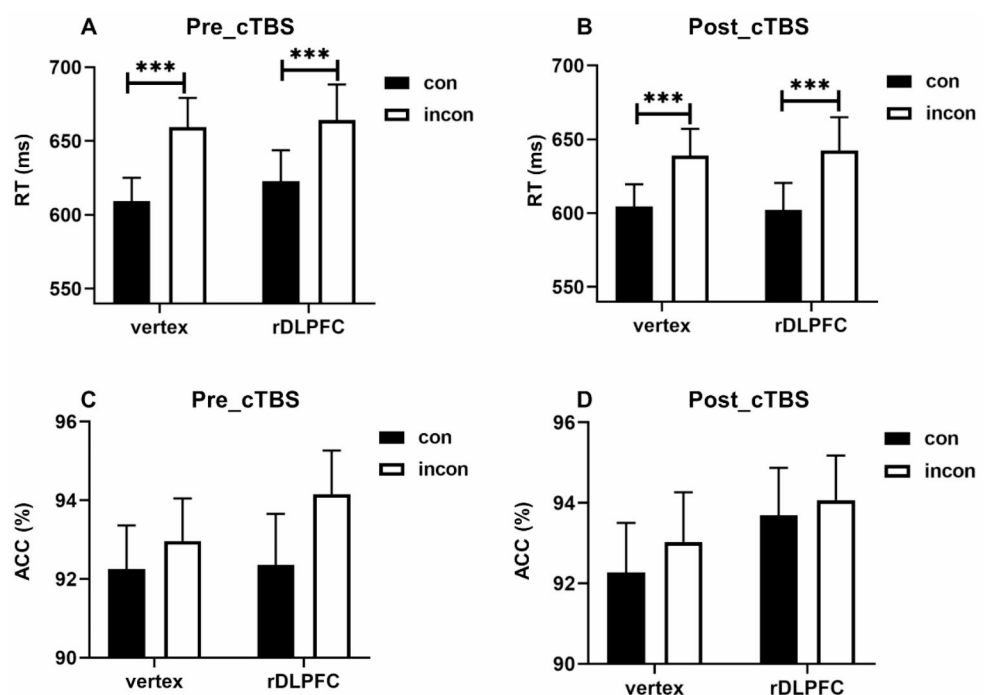
that the cTBS over the rDLPFC modulates the N2 component. Subsequent two-way 2 (Time) $\times$ 2 (Site) ANOVAs on the Stroop effect of N2 peak amplitude showed a main effect of Site ($F_{(1, 23)} = 6.359$, $p = 0.019$, $\eta_p^2 = 0.217$). Post-hoc t-tests showed that the Stroop effect of the N2 component was reduced after the cTBS over the rDLPFC, compared to the vertex stimulation ($t(23) = -3.178$, $p = 0.024$), suggesting that the modulation of the rDLPFC by the cTBS affected the Stroop effect of the N2 component. The correlation analysis found that the Stroop effect of N2 peak amplitude was significantly positively correlated with the Stroop effect of accuracy before the cTBS over the rDLPFC ($r = 0.441$, $P = 0.031$), suggesting that a larger N2 amplitude was associated with higher accuracy in performing the Stroop task. All the details are shown in Fig. 3. For the N2 latency, a significant main effect of Type was observed in three-way ANOVAs ($F_{(1, 23)} = 13.554$, $p = 0.001$, $\eta_p^2 = 0.371$), indicating the longer latencies in incongruent trials than congruent trials.

Time-frequency Results

The hypothesis-driven Oscillation Results

For the hypothesis-driven theta oscillation, the averaged topographic maps in the 90–150ms time window are shown in Fig. 4A. The three-way 2 (Time) $\times$ 2 (Type) $\times$ 2 (Site) ANOVAs revealed an interaction between Type and Site ($F_{(1, 23)} = 4.664$, $p = 0.041$, $\eta_p^2 = 0.169$), with a decrease in the incongruent trials than congruent ones after the rDLPFC stimulation ($t(23) = 2.146$, $p = 0.043$). Subsequent two-way 2 (Time) $\times$ 2 (Site) ANOVAs on the Stroop effect of

Fig. 2 The behavior results. **A–B:** mean response times before and after the cTBS stimulation. **C–D:** mean accuracies before and after the cTBS stimulation. cTBS: continuous theta burst stimulation. Pre_cTBS: before the cTBS stimulation. Post_cTBS: after the cTBS stimulation. RT: response time. ACC: accuracy. con: congruent. incon: incongruent. Error bars represent the standard error of the mean (SEM). Asterisks mark significant paired sample t-test ($***p < 0.001$)



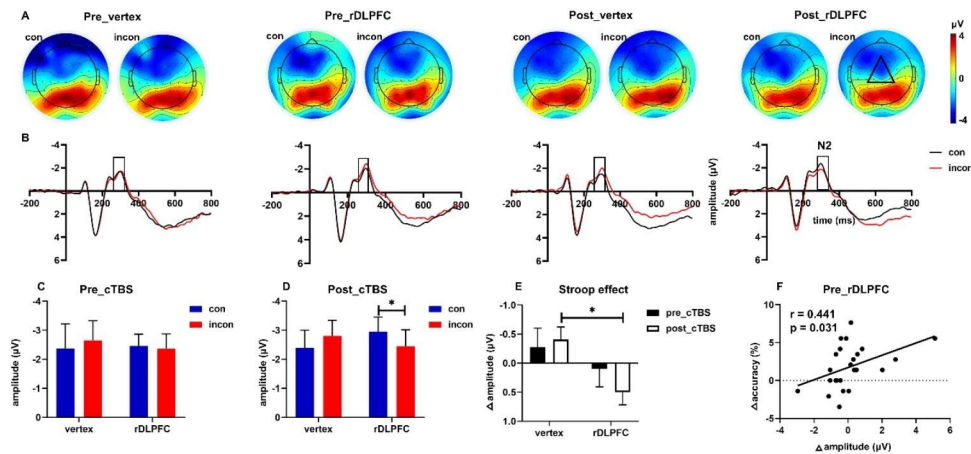


Fig. 3 The results of the N2 component. **A:** The topographic maps of the N2 component between 250–320ms, and the electrodes with black lines are defined as regions of interest (ROIs). **B:** The waveforms within the ROIs, the black lines show the time window of the N2 component. **C–D:** the peak amplitudes of the N2 component before and after the cTBS stimulation. **E:** Stroop effect of N2 component. **F:** The correlation relationship of the Stroop effect between N2 peak amplitude and accuracy before the rDLPFC stimulation. cTBS: con-

tinuous theta burst stimulation. Pre_vertex: before the cTBS over the vertex. Pre_rDLPFC: before the cTBS over the rDLPFC. Post_vertex: after the cTBS over the vertex. Post_rDLPFC: after the cTBS over the rDLPFC. Pre_cTBS: before the cTBS stimulation. Post_cTBS: after the cTBS stimulation. rDLPFC: the right dorsolateral prefrontal cortex. con: congruent. incon: incongruent. Error bars represent the standard error of the mean (SEM). Asterisks mark significant paired sample t-test (* $p < 0.05$)

the theta oscillation showed a main effect of Site ($F_{(1, 23)} = 4.664, p = 0.041, \eta_p^2 = 0.169$), with reduced Stroop effect on the rDLPFC than on the vertex, indicating that the modulation of the rDLPFC activity by cTBS affected the theta oscillation. All the details are shown in Fig. 4C–E.

Figure 4B shows the topographic maps of alpha oscillations between 500–700ms. The three-way 2 (Time) $\times$ 2 (Type) $\times$ 2 (Site) ANOVAs showed an interaction between Type and Site ($F_{(1, 23)} = 5.316, p = 0.030, \eta_p^2 = 0.188$). Crucially, a three-way interaction was found ($F_{(1, 23)} = 5.157, p = 0.033, \eta_p^2 = 0.183$). Then, post hoc t-tests showed that the alpha oscillations were reduced in incongruent trials than congruent ones after stimulating the rDLPFC ($t(23) = 2.495, p = 0.020$), indicating that the rDLPFC stimulation enhanced the alpha desynchronization for incongruent trials than congruent trials, as shown in the middle of Fig. 4G. For the Stroop effect of alpha oscillation, the two-way 2 (Time) $\times$ 2 (Site) ANOVAs showed a significant main effect of Site ($F_{(1, 23)} = 5.316, p = 0.030, \eta_p^2 = 0.188$), with reduced Stroop effect on the rDLPFC than on the vertex. Crucially, a significant two-way interaction was found ($F_{(1, 23)} = 5.157, p = 0.033, \eta_p^2 = 0.183$). The rDLPFC stimulation reduced the Stroop effect of alpha oscillation, compared to before the stimulation ($t(23) = 2.413, p = 0.024$) and the vertex stimulation ($t(23) = 3.242, p = 0.004$), as shown in Fig. 4H. These results indicated that the cTBS over the rDLPFC modulated the Stroop effect of the alpha oscillation. The Stroop effect of alpha oscillation was significantly positively correlated with the Stroop effect of RT after the application of cTBS to the vertex ($r = 0.441, p = 0.031$),

suggesting that individuals who exhibit greater Stroop interference in their alpha oscillations also tend to experience greater Stroop interference in RTs after the vertex stimulation, as shown in Fig. 4I. No other significant differences or correlation were observed.

Considering that the above alpha oscillation was observed in the left hemisphere, the hemispheric difference of the alpha oscillation was analyzed for exploratory purposes. We extracted the alpha oscillation from the right homologous regions and then performed statistical analysis on the Stroop effect of alpha oscillation. The three-way 2 (Time) $\times$ 2 (Site) $\times$ 2 (Hemi: right vs. left) ANOVAs found a main effect of Hemi ($F_{(1, 23)} = 11.432, p = 0.003, \eta_p^2 = 0.332$) and an interaction between Hemi and Time ($F_{(1, 23)} = 11.166, p = 0.003, \eta_p^2 = 0.327$). Notably, a three-way interaction was found ($F_{(1, 23)} = 8.165, p = 0.009, \eta_p^2 = 0.262$). Subsequent post hoc t-tests found that the rDLPFC stimulation reduced the Stroop effect of alpha oscillation for left hemisphere, compared to the right hemisphere ($t(23) = 4.207, p < 0.001$) and the vertex stimulation ($t(23) = 3.242, p = 0.004$), indicating mediation of the left parieto-occipital alpha oscillations by the rDLPFC stimulation, as shown in Fig. 5B. After calculating the hemispheric differences (right-left), the two-way 2 (Time) $\times$ 2 (Site) ANOVAs revealed a main effect of Time ($F_{(1, 23)} = 11.166, p = 0.003, \eta_p^2 = 0.327$). Crucially, an interaction was found ($F_{(1, 23)} = 8.165, p = 0.009, \eta_p^2 = 0.262$), with increased hemispheric differences after the rDLPFC stimulation than before the rDLPFC stimulation ($t(23) = -3.655, p = 0.001$) as well as than the vertex stimulation ($t(23) = -2.451, p = 0.022$), suggesting a significant

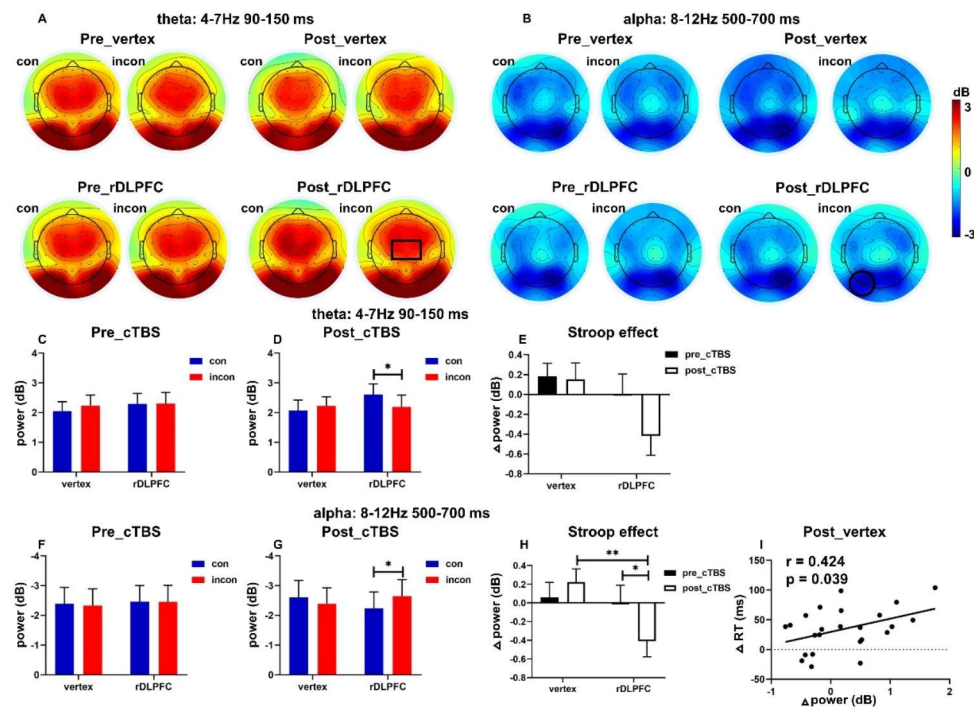


Fig. 4 The results of hypothesis-driven oscillation analysis. A-B: The topographic maps of theta oscillations (90–150ms) and alpha oscillations (500–700ms), and the electrodes with black lines are defined as regions of interest (ROIs). C-D: theta oscillation before and after the cTBS stimulation. E: Stroop effect of theta oscillation. F-G: alpha oscillation before and after the cTBS stimulation. H: Stroop effect of alpha oscillation. I: The correlation relationship of the Stroop effect between alpha oscillation and RT after the vertex stimulation. cTBS:

continuous theta burst stimulation. Pre_vertex: before the cTBS over the vertex. Pre_rDLPFC: before the cTBS over the rDLPFC. Post_vertex: after the cTBS over the vertex. Post_rDLPFC: after the cTBS over the rDLPFC. Pre_cTBS: before the cTBS. Post_cTBS: the posttest after the cTBS. con: congruent. incon: incongruent. Error bars represent the standard error of the mean (SEM). Asterisks mark significant paired sample t-test (* $p < 0.05$, ** $p < 0.01$)

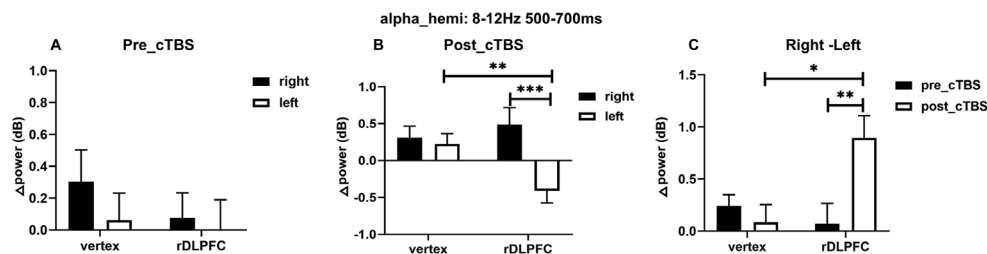


Fig. 5 The hemispheric differences on the Stroop effects of alpha oscillations. A-B: Stroop effect of alpha oscillation in the left and right hemispheres before and after the cTBS stimulation. C: The hemispheric differences (right-left) of alpha oscillation on the Stroop effect.

cTBS: continuous theta burst stimulation. Pre_cTBS: before the cTBS. Post_cTBS: after the cTBS. Error bars represent the standard error of the mean (SEM). Asterisks mark significant paired sample t-test (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$)

hemispheric difference after the rDLPFC stimulation by the cTBS, as shown in Fig. 5C.

The data-driven Oscillation Results

For the data-driven oscillation analysis, the 2(Type)-by-2(Site) factorial design introduced the frontal-central-temporal theta oscillations (F8, FT8, T8, C6, TP8, CP6, CP4) between 823–1408ms. The three-way 2 (Time) $\times$ 2 (Type) $\times$ 2 (Site) ANOVAs showed a three-way interaction ($F_{(1, 23)} = 12.084$, $p = 0.002$, $\eta_p^2 = 0.344$). Further post hoc t-tests

showed that the rDLPFC stimulation increased theta activity in congruent trials than the vertex stimulation ($t(23) = -2.147$, $p = 0.043$), and the incongruent trials had greater theta oscillation than congruent trials on the vertex ($t(23) = -3.566$, $p = 0.002$), showing that the rDLPFC stimulation modulated the post-response theta oscillation for the congruent trials, as shown in Fig. 6D. Additionally, a significant interaction ($F_{(1, 23)} = 12.084$, $p = 0.002$, $\eta_p^2 = 0.344$) was showed in the two-way 2 (Time) $\times$ 2 (Site) ANOVAs for the Stroop effect of the theta activity, with reduced Stroop effect of theta oscillation after the rDLPFC stimulation than vertex

stimulation ($t(23) = 3.703, p = 0.001$) and increased Stroop effect after the cTBS over the vertex than before cTBS ($t(23) = -2.750, p = 0.011$), indicating that the rDLPFC stimulation modulated the Stroop effect of the post-response theta oscillation, as shown in Fig. 6E.

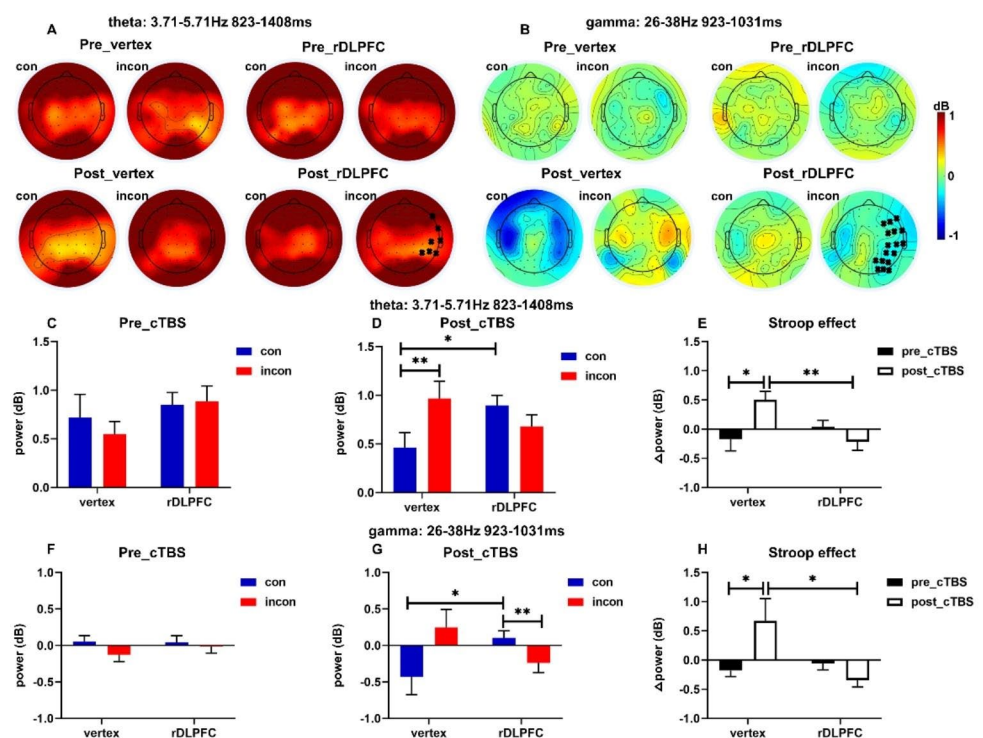
The 2 (Time)-by-2 (Site) factorial design for the Stroop effect displayed the gamma oscillation (26–38 Hz) between 929–1031ms across the frontal-central-temporal electrodes (F4, F6, F8, FC4, FC6, FT8, C4, C6, T8, CP4, CP6, P2, P4, P6, PO4, PO6, PO8). The three-way ANOVAs revealed a two-way interaction between Type and Site ($F_{(1,23)} = 4.662, p = 0.042, \eta_p^2 = 0.169$) and a three-way interaction ($F_{(1,23)} = 10.917, p = 0.003, \eta_p^2 = 0.322$). Subsequent post hoc t-tests found a decrease in gamma activity in incongruent trials than congruent trials after the rDLPFC stimulation ($t(23) = 2.965, p = 0.007$) and an increase in congruent trials after the rDLPFC stimulation than vertex stimulation ($t(23) = -2.130, p = 0.044$), showing that modulation of the rDLPFC activity increased the post-response gamma oscillations for congruent trials, as shown in Fig. 6G. Moreover, the main effect of Site ($F_{(1,23)} = 4.662, p = 0.042, \eta_p^2 = 0.169$) and a two-way interaction ($F_{(1,23)} = 10.917, p = 0.003, \eta_p^2 = 0.322$) were found by the two-way 2 (Time) $\times$ 2 (Site) ANOVAs for the Stroop effect of the gamma activity. Post hoc t-tests showed a reduced Stroop effect after the rDLPFC stimulation than vertex stimulation ($t(23) = -2.127, p = 0.044$) and an increased Stroop effect after the cTBS over the vertex than before the cTBS stimulation ($t(23) = 2.818, p = 0.010$), indicating that the rDLPFC stimulation modulated

the Stroop effect of the post-response gamma oscillation, as shown in Fig. 6H.

Discussion

The study investigated the causal role of the rDLPFC on conflict processing using the color-word Stroop task with combined cTBS and EEG. Although the cTBS did not induce significant changes in behavioral performance, the classic Stroop effect was observed with slower RT for incongruent trials than congruent trials. Importantly, the rDLPFC stimulation modulated the physiological correlates of conflict processing. Firstly, the application of cTBS to the rDLPFC modulated the conflict monitoring-related frontal-central N2 component and theta oscillations. Specifically, reduced N2 amplitude and theta activity were observed for the incongruent trials than congruent trials after the rDLPFC stimulation, and the Stroop effects of N2 were reduced after the rDLPFC stimulation. Furthermore, the cTBS over the rDLPFC modulated the conflict resolution-related parieto-occipital alpha oscillation, with decreased alpha oscillation on incongruent trials than congruent trials and decreased Stroop effect after the rDLPFC stimulation than vertex stimulation. Additionally, we exploratively found that the cTBS over the rDLPFC led to significant hemispheric differences for alpha oscillation, with a stronger Stroop effect for the left hemisphere than the right hemisphere. Finally, the data-driven oscillation analysis showed a significant reduction

Fig. 6 The results of data-driven oscillation analysis. A–B: The topographic maps of theta oscillation (823–1408ms) and gamma oscillation (923–1031ms). C–D: theta oscillation before and after the cTBS stimulation. E: Stroop effect of theta oscillation. F–G: gamma oscillation before and after the cTBS stimulation. H: Stroop effect of gamma oscillation. cTBS: continuous theta burst stimulation. Pre_vertex: before the cTBS over the vertex. Pre_rDLPFC: before the cTBS over the rDLPFC. Post_vertex: after the cTBS over the vertex. Post_rDLPFC: after the cTBS over the rDLPFC. Pre_cTBS: before the cTBS. Post_cTBS: after the cTBS. con: congruent. incon: incongruent. Error bars represent the standard error of the mean (SEM). Asterisks mark significant paired sample t-test (* $p < 0.05$, ** $p < 0.01$)



of Stroop effects for post-response theta and gamma oscillations after the rDLPFC stimulation compared to vertex stimulation.

Effects of cTBS on Task Performance during Conflict Processing

In the current study, the classical Stroop effect was observed on the rDLPFC and the vertex, with slower RTs in incongruent trials than congruent ones, which was consistent with previous studies (Anderkova et al. 2018; Ergen et al. 2014; Heidlmayr et al. 2020). Our results once again demonstrated that the Stroop effect was stable in behavioral outcomes, showing greater conflict in the incongruent trials. Furthermore, the cTBS over the rDLPFC did not significantly change the Stroop effect of ACC and RT. A previous study applied the cTBS to the rDLPFC and reported no significant changes in the Stroop effect on RT after the stimulation relative to before the stimulation in a keypress Stroop task (Anderkova et al. 2018). This aligns with our results, indicating that modulation of the rDLPFC activity by cTBS has no change in the behavioral performance, as measured by the Stroop effect. An earlier study found that the cTBS over the rDLPFC significantly increased the Stroop effect for men with pathological gambling, compared to sham stimulation, highlighting a critical involvement of the rDLPFC in conflict resolution (Zack et al. 2016). Notably, this study provided a total of 900 pulses during cTBS stimulation, more than our study and (Anderkova et al. 2018)'s study (600 pulses). The number of pulses, one of the important parameters of the cTBS protocol, had an impact on the after-effect of cTBS (McCalley et al. 2021; Wischniewski and Schutter 2015). Therefore, one of the possible reasons for the absence of the moderating effects of cTBS on the Stroop effect is that the pulse numbers delivered by cTBS did not sufficiently change the cortical excitability of the rDLPFC to cause significant changes in behavior. More appropriate parameters of the cTBS protocol would help us to better understand the causal role of the rDLPFC in conflict resolution.

Altered N2 Component and theta Oscillation of Conflict Monitoring by cTBS

The cTBS over the rDLPFC modulated the frontal-central N2 component. Specifically, the application of cTBS to the rDLPFC resulted in a decrease in amplitude of the N2 component for incongruent trials than congruent ones and a reduction of the Stroop effect than the vertex stimulation. The frontal N2 component was often considered as an index of conflict, which was involved in the conflict monitoring process (Heidlmayr et al. 2020; Larson et al. 2014). The

amplitude of the N2 component was more negative in incongruent trials relative to congruent trials (Boenke et al. 2009; Overbye et al. 2021; Pan et al. 2016; W. Wang et al. 2021), indicating stronger cognitive control in a conflict situation. Moreover, the N2 component could be modulated by repetitive TMS (Li et al. 2017; Ware et al. 2021) and transcranial direct current stimulation (Dubreuil-Vall et al. 2019) applied to the DLPFC. The current results found that the cTBS over the rDLPFC could affect the conflict detection-related N2 component through the tuning of cognitive control.

The rDLPFC stimulation modulated the early frontal-central theta oscillation. The lower theta oscillation was observed in incongruent trials than in congruent trials only after the rDLPFC stimulation. In the Stroop task, frontal theta oscillations were often associated with the detection of interference and inhibition of responses to task-irrelevant features (Eschmann et al. 2018; Hanslmayr et al. 2008; Itthipuripat et al. 2019; Oehrns et al. 2014; Tang et al. 2013). The theta activity increased more in high-conflict trials than in low-conflict trials (Eschmann et al. 2018; Itthipuripat et al. 2019) and increased linearly with increasing interference (Hanslmayr et al. 2008). The current results found the cTBS over the rDLPFC changed the theta activity between incongruent and congruent trials, indicating that the rDLPFC was involved in the conflict monitoring process in a top-down manner.

Altered Alpha Oscillation of Conflict Resolution by cTBS

The application of cTBS to the rDLPFC modulated the parieto-occipital alpha oscillations. The incongruent trials had lower alpha oscillations than congruent trials after the rDLPFC stimulation. Subsequent analysis showed that the rDLPFC stimulation significantly reduced the Stroop effect relative to before cTBS and relative to the vertex stimulation. Previous studies found the decreased alpha power over parieto-occipital electrodes on incongruent trials compared to congruent trials (Jiang et al. 2015, 2018). The alpha oscillation is usually associated with the process of task-irrelevant information (Marshall et al. 2016; Payne and Sekuler 2014), and is suggested to reflect inhibitory control of motor response tendencies during conflict resolution with the Stroop task (Hwang et al. 2014; Sadaghiani and Kleinschmidt 2016). Moreover, the TMS over the prefrontal cortex disrupted the alpha lateralization during the shifting of visuospatial attention (Sauseng et al. 2011). The current study suggests that the cTBS over the rDLPFC modulates the parieto-occipital alpha activity with the Stroop task, indicating the involvement of rDLPFC in conflict resolution through the process of task-irrelevant information during incongruent trials.

Notably, the reported alpha modulation was only observed in the left hemisphere. To explore the hemispheric differences, we calculated the Stroop effect for the left and right hemispheres and then performed statistical analysis. However, no significant hemispheric difference was found in the Stroop effect of alpha oscillations in the control conditions (before and after vertex stimulation, before rDLPFC stimulation). Previous EEG studies have reported alpha lateralization in visual tasks, where more negative alpha activity is observed in the contralateral side to the attended position, indicating the inhibitory control of the unattended position (Benedek et al. 2014; Gallotto et al. 2020; Haegens et al. 2011; Thut et al. 2006). However, since our stimuli were presented at the center of the screen, we did not expect to observe alpha lateralization in the control conditions, which aligns with our current findings. In addition, we found that the rDLPFC stimulation reduced the Stroop effect of alpha oscillation in the left hemisphere more than the right hemisphere and the vertex stimulation, indicating that the rDLPFC stimulation enhances inhibitory control in the left parieto-occipital areas. One possible explanation for this finding is the presence of an interhemispheric compensatory effect (Hartwigsen 2018). It is plausible that when rDLPFC activity is inhibited by cTBS stimulation, activity in the left brain region is enhanced as a compensatory mechanism to counteract the disruption caused by cTBS. The current results do not provide strong support for these explanations. Future studies could further explore this compensatory effect using a combination of TMS and fMRI. Overall, our findings suggest that the rDLPFC is involved in conflict resolution by inhibiting the processing of irrelevant information, with a specific impact on alpha oscillations in the left hemisphere.

Altered post-response theta and Gamma Oscillations of Conflict Adaptation by cTBS

The data-driven oscillation analysis revealed the theta oscillation (823–1408ms) and gamma oscillation (923–1031ms) after the responses (averaged RTs: 500–700ms). The incongruent trials had stronger theta oscillation than congruent trials after the application of vertex stimulation and the application of the rDLPFC stimulation increased the theta power in congruent trials compared to vertex stimulation. Previous studies found the theta oscillations were increased after the incorrect response (Cavanagh et al. 2009; Mojsa-Kaja et al. 2017), and the increased power can be partially predictive of improved performance on the next trial (Cohen and van Gaal 2013; Valadez and Simons 2018). Additionally, the inter-trial frontal theta oscillations were increased in preparation for control-demanding situations (Cooper et al. 2017; Kaiser and Schutz-Bosbach 2019). Our results suggest that

the cTBS over the rDLPFC enhances the proactive adjustment after response for congruent trials. For gamma oscillation, reduced power was found in the incongruent trials than in the congruent trials after the rDLPFC stimulation. The gamma oscillations were related to cognitive control, with greater power when cognitive control is stronger (Farzan et al. 2009, 2012). In the Stroop task, higher gamma oscillations were reported after incongruent trials (Bartoli et al. 2018), and post-response gamma power in a conflicting trial predicted shorter RTs in an upcoming conflict trial (Oehrn et al. 2014), which suggests that gamma oscillations after responses are related to the adjustment of cognitive control to conflict. Thus, the current results may indicate that the rDLPFC stimulation influences the cognitive control adjustment to conflict.

The Limitation

Several limitations of the present study should be discussed. First, the method of cTBS-EEG was an offline technique, which was selected to explore the effects of cTBS on behavioral performance and physiological correlates of conflict processing in the current study. Although the cTBS was suggested to have a certain duration of after-effects (Huang et al. 2005; Stefan et al. 2008), individual differences between participants may lead to the inability to accurately control the duration of cTBS effects, which may lead to a certain impact on the results. Second, the stimulation intensity of the cTBS was slightly different between the participants, which may lead to possible individual differences. The consistent or individually calibrated stimulation intensities could be considered for future studies. Third, previous studies found that neural communication patterns played an important role in conflict processing (Bartoli et al. 2018; Oehrn et al. 2014), whereas the current study only explored the effects of the rDLPFC stimulation on conflict processing with ERP and time-frequency analyses. Future studies could consider neural communication analysis to achieve a comprehensive understanding of conflict processing. Finally, the present study did not undergo pre-registration before commencing formal experimentation. Future studies should consider pre-registration to confirm the soundness and scientific validity of the study. By pre-registering a study, researchers can establish a transparent framework that outlines their hypotheses, methods, and analysis plans before data collection, thereby minimizing the potential for bias and enhancing the credibility of the findings.

Conclusion

This study applied behavioral experiments, cTBS, and EEG to investigate the causal role of the right DLPFC in mediating the conflict process. The results found that modulation of the rDLPFC activity affected the physiological correlate of conflict processing. Specifically, the cTBS over the rDLPFC modulated the conflict monitoring-related N2 component and theta oscillation, conflict resolution-related alpha oscillation and conflict adjustment-related theta and gamma oscillation. Exploratorily, the cTBS over the rDLPFC resulted in a significant hemispheric difference in alpha oscillation. The current study revealed the electrophysiological mechanism of conflict processing mediated by the DLPFC and provided a relatively new perspective on conflict processing.

CRediT authorship contribution statement.

Ping Xu: conceptualization, methodology, investigation, Data acquisition, Data curation, formal analysis, visualization, writing original draft, writing review & editing. Song Wang: Data acquisition. Yulu Yang: Data acquisition. Bishal Guragai: English grammar check and writing review. Qiu-zhu Zhang: writing review. Junjun Zhang: conceptualization, investigation, writing review & editing. Zhenlan Jin: conceptualization, investigation, writing review & editing. Ling Li: conceptualization, methodology, supervision, writing review & editing, Funding acquisition.

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Author Contributions A: conceptualization, methodology, investigation, Data acquisition, Data curation, formal analysis, visualization, writing original draft, writing review & editing. B.C: Data acquisition. Yulu Yang: Data acquisition. D: English grammar check and writing review. E: writing review. F.G: conceptualization, investigation, writing review & editing. H: conceptualization, methodology, supervision, writing review & editing, Funding acquisition. All authors reviewed the manuscript.

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Data Availability The data that support the findings of this study are available on request from the corresponding author.

Declarations

Competing Interests The authors declare no competing interests.

Conflict of Interest The authors declare that they have no competing interests.

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