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RESEARCH ARTICLE

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Online and offline effects of parietal 10 Hz repetitive transcranial magnetic stimulation on working memory in healthy controls

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Abstract

Parietal alpha activity shows a specific pattern of phasic changes during working memory. It decreases during the encoding and recall phases but increases during the maintenance phase. This study tested whether online rTMS delivered to the parietal cortex during the maintenance phase of a working memory task would increase alpha activity and hence improve working memory. Then, 46 healthy volunteers were randomly assigned to two groups to receive 3-day parietal 10 Hz online rTMS (either real or sham, 3600 pulses in total) that were time-locked to the maintenance phase of a spatial span task (180 trials in total). Behavioral performance on another spatial span task and EEG signals during a change detection task were recorded on the day before the first rTMS (pretest) and the day after the last rTMS (posttest). We found that rTMS improved performance on both online and offline spatial span tasks. For the offline change detection task, rTMS enhanced alpha activity within the maintenance phase and improved interference control of working memory at both behavioral (K score) and neural (contralateral delay activity) levels. These results suggested that rTMS with alpha frequency time-locked to the maintenance phase is a promising way to boost working memory.

KEYWORDS

alpha oscillation, contralateral delay activity, parietal cortex, repetitive transcranial magnetic stimulation, working memory

1 | INTRODUCTION

Working memory is a high-level cognitive function characterized by limited capacity, so irrelevant information needs to be suppressed in order to ensure that relevant information enters and is maintained in the working memory system (Bonnefond & Jensen, 2012; Hakim et al., 2021; Noonan et al., 2016; Schroeder et al., 2018). The suppression of irrelevant information is called interference control, whose exact mechanism is still unknown. Recent electrophysiological studies in healthy adults have consistently pointed to the importance of

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parietal alpha oscillation (de Vries et al., 2020; Erickson et al., 2019; Poch et al., 2018; Schroeder et al., 2018; Wianda & Ross, 2019). Parietal alpha activity changes dynamically across phases of working memory (i.e., encoding, maintenance, and recall) and is modulated by cognitive burden of interference control (Hakim et al., 2021; Schroeder et al., 2018). Therefore, it seems possible that brain stimulation with alpha frequency, a method that can enhance parietal alpha power (Capotosto et al., 2015; Luber et al., 2007; Sauseng et al., 2009; Thut et al., 2011), may improve working memory.

Sauseng et al., 2009 were among the early researchers to recognize the importance of parietal alpha (8–13 Hz) oscillation. In their original study, they cued participants' attention to either the left or right visual hemifield and found that alpha power increased in the posterior hemisphere ipsilateral to the attended visual hemifield (task-irrelevant hemisphere), but decreased in the posterior hemisphere contralateral to the attended visual hemifield (task-relevant hemisphere). Since then, researchers (Jensen & Mazaheri, 2010) have proposed the alpha inhibition hypothesis that increasing alpha power contributes to the suppression of irrelevant information while decreasing alpha power contributes to the facilitation of relevant information. Recently, studies on working memory using different tasks without interference control burden (e.g., working memory span task, Sternberg task, and change detection task) also supported the same hypothesis (Bahramisharif et al., 2018; Emrich et al., 2017; Erickson et al., 2019; Wianda & Ross, 2019). They found that decreased parietal alpha power during the encoding phase facilitated the processing of to-be-remembered information, whereas increased parietal alpha power during the maintenance phase suppressed the processing of new information and thereby protected information already held online from interference.

Because brain stimulation with alpha frequency can only enhance, but cannot weaken, alpha activity (Emrich et al., 2017; Hamidi et al., 2009; Johnson et al., 2010; Sauseng et al., 2009), the maintenance phase becomes the only possible target for parietal brain stimulation with alpha frequency in order to improve working memory. Indeed, previous studies that delivered online parietal 10 Hz rTMS during phases other than the maintenance phase (e.g., Hamidi et al., 2009; Kemmerer et al., 2022) did not improve working memory. In contrast, two of the three studies that delivered brain stimulation with alpha frequency during the maintenance phase showed positive results. Specifically, both Sauseng et al. (2009) and Riddle et al. (2020) delivered online parietal 10 Hz rTMS during the maintenance phase of a working memory task and found improved working memory at the visual hemifield ipsilateral to rTMS. In contrast, Emrich et al. (2017) also delivered online parietal 10 Hz rTMS during the maintenance phase of a working memory task, but did not find improvement in working memory. One major difference between the studies of Sauseng et al. and Riddle et al. and that of Emrich et al. is that the former two studies used a working memory task with interference control burden, whereas the latter used a task without interference control burden.

To test whether a lack of interference control burden was responsible for Emrich et al.'s (2017) lack of rTMS-induced improvement in working memory, we performed this EEG study. In addition, our study also aimed to test whether any online effect of rTMS, if found, would be generalized to offline tasks (either similar or dissimilar to the online task). This study randomly allocated 46 healthy volunteers into two groups to receive either real or sham parietal rTMS with alpha frequency during the maintenance phase while performing a working memory span task. Participants performed the task across three continuous days. On the day before the first rTMS and the day after the last rTMS, we recorded behavioral performance on a spatial span task similar to the one used during training and collected EEG data during another working memory task (a change detection task). Based on the alpha inhibition hypothesis, we hypothesized that online 10 Hz rTMS time-locked to the maintenance phase would improve working memory (both maintenance and interference control).

2 | METHODS

2.1 | Subjects

Forty-six healthy students aged 18–30 years were recruited from Beijing Normal University. This was a between-subjects design study. All subjects were naïve to rTMS. They were also interviewed by experienced psychiatrists to exclude current or previous psychiatric or neurological diseases. Subjects with contraindications to TMS (e.g., family history of epilepsy) were also excluded. All participants in the study were right-handed and had normal or corrected-to-normal visual acuity, as well as normal color vision. This study was approved by Beijing Normal University Institutional Review Board. All subjects provided their written informed consents before the experiment and received equal monetary compensation.

2.2 | Procedure

The experiment lasted for five consecutive days. Subjects were assigned randomly to either real ($n = 23$) or sham ($n = 23$) rTMS group following a computer-generated list of random numbers before the experiment. As shown in Figure 1, on the first day of the experiment, subjects received pretests at both behavioral (a spatial span task that was revised from the rTMS task) and EEG (during a change detection task) levels. Afterward, subjects received real or sham online-rTMS (TMS pulses were given while participants were performing a spatial span task) for three consecutive days (from day 2 to day 4). On the last day of the experiment (day 5), subjects received posttests, which were the same as the pretests.

2.3 | Online rTMS intervention (during the spatial span task)

In this study, 10 Hz online rTMS was applied on the parietal cortex when subjects were performing the spatial span task. This task

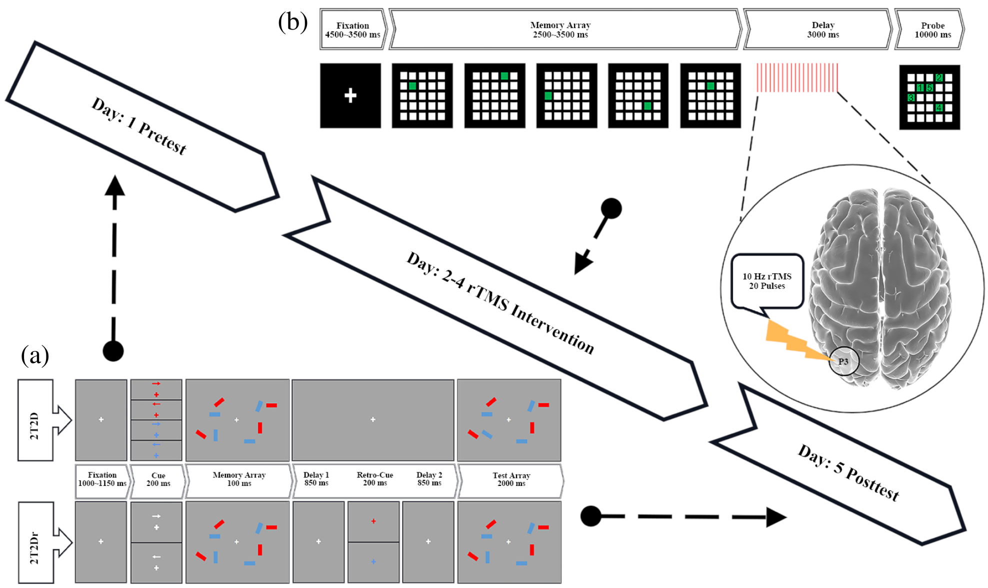

FIGURE 1 Schematic depiction of the procedure of this 5-day's rTMS study. Panel (a) shows the schematic of change detection task for EEG recording at pretest and posttest. Panel (b) shows the schematic of the rTMS that were delivered at the delay period of a spatial span task.

included three conditions with varied memory load (the number of to-be-remembered stimuli varied from 5 to 7). Each condition had 20 trials. We divided the total 60 trials into two sessions (30 trials for each session, i.e., 10 trials for each condition), with a 30-min interval between sessions. As shown in Figure 1, stimuli were green-colored squares presented sequentially in a 5 × 5 empty grid on a computer screen. Each stimulus was presented for 500 ms. After the presentation of the last stimulus, there was a 3 s delay (maintenance) period followed by an empty grid. Subjects were required to remember both the location and the order of all stimuli and to tap, using a computer mouse, the squares in the empty grid to indicate the locations of stimuli in the order they were presented. We then calculated the average number of correctly remembered squares (for both the order and spatial position) to indicate individuals' performance on each condition.

During the first 2 s of the delay period of each trial, 20 TMS pulses were administrated at P3 (Yamanaka et al., 2010) of the international 10–20 EEG system. For each day, subjects performed 60 trials in total that were divided into two sessions (30 trials for each session, i.e., 10 trials for each memory load condition) with a 30-min interval between sessions. Therefore, each subject received 600 pulses (20 × 30) per session, 1200 pulses (600 × 2) per day, resulting in 3600 pulses in total (1200 × 3) during the three consecutive days.

To deliver rTMS, a 70 mm figure-of-eight coil connected to a Magstim Rapid2 stimulator (MagStim, Whitland, UK) was used. For the real rTMS group, the coil was held tangential to the scalp with the handle pointing 45° posterior. For the sham rTMS group, the coil was rotated 90° about the axis of the handle with one wing in contact with the scalp. To avoid sound interference produced by rTMS, subjects wore earplugs during the whole session. All the subjects were naive to the TMS, thus they were blind to real and sham rTMS. Moreover, the stimulation intensity was determined as 100% of the resting motor threshold (rMT) that was measured as the lowest intensity needed to evoke motor potentials from the first dorsal interosseus muscle with a peak-to-peak amplitude greater than 50 μV after at least 5/10 trials.

Our rTMS protocols were within the safety limits (Rossi et al., 2020). No subject reported any atypical discomfort or symptoms either during or after the experiment.

2.4 | EEG data acquisition and processing

EEG signals during the change detection task (a widely used measure for both working memory maintenance and interference control process) were recorded at both pretest (day 1) and posttest (day 5). The task was revised from a previous study (Vogel et al., 2005) and was presented on an LCD computer (1024 × 768 pixels, 120 Hz refresh rate) with a homogeneous gray background. Stimuli were bilaterally presented red or blue bars (0.69° × 0.23°) with varied orientations (0°, 45°, 90°, 135°, and 180°). Of the four conditions (200 trials per condition, 800 trials in total), three were reported in Vogel et al.'s study: two targets to be remembered with two distractors (2T2D), two targets with no distractors to be ignored (2T), and four targets to be remembered without distractors (4T). As shown in Figure 1a, after an intertrial interval (1000–1150 ms), each trial began with a centrally placed fixation cross accompanied by an arrow above it (the cue, 200 ms). Subjects were instructed to keep their eyes on the cross during the whole task. Both the fixation cross and the arrow were red- or blue-colored. Subjects were required to pay attention to the target bars that were in the same color and within the hemifield as indicated by the arrow. Subjects were instructed to remember the orientations of target bars and ignore distractor bars (if any). After a delay phase (1900 ms, during which a white fixation cross was presented centrally on the screen), a test array was presented for 2000 ms and subjects were instructed to report whether the orientations of all target bars at the attended side were the same as those of the memory array. In addition to the three conditions mentioned above, we included a retro-cue condition (2T2Dretrocue). As shown in Figure 1, each trial of this condition also started with a centrally placed fixation cross and an arrow above it, but both were white-colored indicating that subjects should pay attention to all four bars on the hemifield indicated by the arrow. Memory array was then followed by a short delay period (the first of two delays, 850 ms, during which a white fixation cross was presented centrally on the screen). Afterward, a red- or blue-colored fixation cross (200 ms) was presented to indicate that subjects should remember the bars with the same color as the fixation cross. The second delay period (850 ms, during which a white fixation cross was presented centrally on the screen) appeared and was followed by a test array. For all four conditions, subjects were instructed to press the "1" key for no-change trials and the "3" key for change trials. The number of no-change trials was the same as that of the change trials. We used K score to reflect individuals' performance on this task. K score was calculated using the following formula by Cowan (2001): $K = S \times (H - F)$, where S is the number of items to be remembered, H the observed hit rate, and F the false alarm rate.

EEG signals were recorded with a 64-channel SynAmps RT system (Neuroscan, El Paso, TX). During recording, subjects sat in a comfortable chair in a dim, electrically shielded chamber. Electrode impedance was kept well below 5 kΩ. EEG signals were band-pass filtered at DC to 200 Hz, online referenced to left mastoid and digitized at a sampling rate of 1000 Hz. To measure eye movements, the vertical electrooculographies (EOGs) were recorded with electrodes set below and above the left eye and the horizontal EOGs were recorded with electrodes set at outer canthi of each eye.

Offline EEG data processing for subsequent power spectrum analysis (mainly alpha power analysis) and contralateral delay activity (CDA) analysis was conducted in MATLAB (The MathWorks Inc., Natick, MA) using the EEGLAB toolboxes (Delorme & Makeig, 2004) and custom codes. All the analyses shared the same preprocessing. Briefly, EEG data were filtered by a 0.1–30 Hz band-pass filter (6 dB/octave roll-off, FIR filter), down sampled to 256 Hz and rereferenced to the average of all the electrodes. Then, the data were segmented into epochs from 1.5 s before to 2.5 s after the onset of memory array (−1.5 to 2.5 s) and trials of correct responses were extracted for subsequent analyses. Note that we chose a relatively long epoch window to avoid edge artifacts of subsequent power spectral analysis (Reinhart & Nguyen, 2019). Eye-blink related artifacts correction was performed on epoch data using independent component analysis. Epochs were automatically excluded if EEG exceeded ±150 μV at any electrode, the vertical EOG exceeded ±80 μV, or the horizontal EOG exceeded ±50 μV during the delay period. As a result, the average numbers of trials used for further analyses were 168 for the 2T condition, 168 for the 2T2D condition, 147 for the 4T condition, and 152 for the 2T2Dretrocue condition.

CDA analysis was performed following the method of our previous study (Deng et al., 2022). Briefly, we focused our analysis on the delay period (early window: 300–900 ms and late window: 1300–1900 ms) of the preprocessed EEG data on parieto-occipital electrodes (PO3/4, PO5/6, PO7/8) after baseline correction using −1200 to −200 ms prior to the appearance of the memory array. The mean CDA was calculated as the difference in mean amplitudes between the contralateral and the ipsilateral waveforms (contralateral–ipsilateral). The contralateral waveform was calculated by averaging the EEG activity across all right electrodes (PO4, PO6, PO8) of the left-cued trials and that of left electrodes (PO3, PO5, PO7) of the right-cued trials. The ipsilateral waveform was calculated by averaging the EEG activity across all right electrodes (PO4, PO6, PO8) of the right-cued trials and that of left electrodes (PO3, PO5, PO7) of the left-cued trials.

Power spectrum analysis was also limited to parieto-occipital electrodes (PO3/4, PO5/6, PO7/8) as in CDA analysis. The event-related spectral perturbation (ERSP) for each trial was estimated at a frequency range of 2–30 Hz in 1 Hz steps using newtimef () function with short-time Fourier transform of a fixed 500 ms sliding time window (Hanning-tapper). ERSP map was then produced and averaged across all trials and all parietal electrodes. We also specifically analyzed alpha band (8–12 Hz) activity centered on rTMS frequency. This analysis followed the methods of a prior study (Hakim et al., 2021), which did not include baseline correction. We first used eegfiltnew () function to filter the data with an 8–12 Hz band-pass filter and then extracted instantaneous power using hilbert () function. The time window for this analysis was also the same as CDA analysis.

2.5 | Behavioral assessment outside EEG

To test the offline effect of rTMS, we used a variant of the above-mentioned spatial span task as an outcome measure. In this assessment version, two trials were given at each span length starting at span size 3. Testing ceased when the subject failed both trials of a given span size. The length of the longest span recalled correctly was used as the index of spatial working memory capacity.

2.6 | Statistical analysis

Statistical analyses were performed using the SPSS software, Version 22 (IBM Corp, New York, NY). We first conducted chi-square tests, ANOVA, or ANCOVA to check whether the two groups (real rTMS vs. sham rTMS) were comparable in terms of demographic factors and baseline working memory performance. We then used repeated measures ANOVA to test the online effect of rTMS. This analysis included one dependent variable (performance on the spatial span task during rTMS intervention), two within-subjects factors (time: day 2 vs. day 3 vs. day 4; and memory load: 5 vs. 6 vs. 7), and one between-subjects factor (real vs. sham rTMS). Afterward, we conducted a series of repeated measures ANOVA to test the offline effect of rTMS. In the analysis on the revised spatial span task outside EEG, the within-subjects factor was time (pretest vs. posttest) and the between-subjects factor was rTMS (real vs. sham). In the analyses on the change detection task, an additional within-subjects factor (condition: 2T vs. 4T vs. 2T2D vs. 2T2Dretrocue) was included. Significant interaction effects between time and rTMS were followed up by post hoc analyses using paired *t* test with Benjamini–Hochberg false discovery rate for multiple corrections. Finally, we conducted correlation analyses between changes in alpha activity and those in CDA and between changes in CDA and those in K score to test if the improvement in interference control could be attributed to rTMS-related alpha enhancement.

3 | RESULTS

No adverse events or seizures occurred during this study. The two groups were comparable in terms of all demographic factors and both cognitive performance and EEG signals at pretest (see Table 1, all *ps* > .05).

3.1 | Online spatial span task

Data of all 46 subjects entered into this analysis. Three-way repeated measures ANOVA revealed significant main effects of rTMS ($F_{1,44} = 5.207$; $p = .027$), time ($F_{1,43} = 17.000$; $p < .001$), and memory load ($F_{1,43} = 48.790$; $p < .001$), and significant time × memory load interaction effect ($F_{1,41} = 5.455$; $p < .001$), but no other interaction effects (for rTMS × time, $F_{1,43} = 1.502$; $p = .234$; for rTMS × load, $F_{1,43} = 1.379$; $p = .263$). This indicated that real rTMS outperformed sham rTMS at this online task and this effect did not differ across intervention days and task conditions. Consistently, the post hoc analyses showed relatively better performance of the real rTMS group than the sham rTMS group, although these effects did not always achieve significance level (day 2: $t = 2.155$, $p = .055$ for load 5, $t = 2.188$, $p = .055$ for load 6, $t = 1.939$, $p = .059$ for load 7; day 3: $t = 2.773$, $p = .024$ for load 5, $t = 2.216$, $p = .034$ for load 6, $t = 2.194$, $p = .034$ for load 7; day 4: $t = 1.512$, $p = .207$ for load 5, $t = 0.329$, $p = .744$ for load 6, $t = 2.002$, $p = .153$ for load 7, see Figure 2a).

3.2 | Offline spatial span task

To see if the online rTMS effect was maintained on the day after the last rTMS, we conducted a repeated measures ANOVA on the offline task that was performed at pretest and posttest. This analysis showed a significant effect of rTMS on this task, as indicated by a significant rTMS × time interaction effect ($F_{1,44} = 6.156$; $p = .017$), as well as a significant main effect of time ($F_{1,44} = 13.415$; $p = .001$), but no main effect of rTMS ($F_{1,44} = 0.280$; $p = .599$). Post hoc analysis showed significant improvement for the real rTMS group ($t = 4.203$; $p < .001$), but not for the sham rTMS group ($t = 0.866$; $p = .396$) (see Figure 2b).

3.3 | Offline change detection task

Three-way repeated measures ANOVA at the behavioral level (K score) again found a significant effect of rTMS as revealed by the significant interaction effect of rTMS × time ($F_{1,44} = 4.572$; $p = .038$).

TABLE 1 Comparisons of demographic factors and pretest baseline between the real and sham rTMS groups.

	Real		Sham		F or χ^2		p	
Demographic factors								
N	23		23					
Gender (M/F)	8/15		7/16		0.099		.753	
Age (year)	22.40 ± 1.31		21.65 ± 1.49		2.837		.100	
Education (years)	15.35 ± 1.34		14.95 ± 1.43		0.827		.369	
Offline spatial span task	5.95 ± 1.02		6.52 ± 0.84		3.138		.084	
K score								
2T2DR	1.25 ± 0.42		1.26 ± 0.36		0.002		.962	
2T	1.71 ± 0.13		1.65 ± 0.32		0.968		.331	
2T2D	1.56 ± 0.33		1.54 ± 0.32		0.219		.642	
4T	2.22 ± 0.83		2.22 ± 0.67		0.001		.974	
Alpha	300–900	1300–1900	300–900	1300–1900	300–900	1300–1900	300–900	1300–1900
2T2DR	4.14 ± 1.25	4.96 ± 2.10	3.95 ± 1.06	4.61 ± 1.54	0.001	0.047	0.987	0.829
2T	4.17 ± 1.38	6.21 ± 3.32	4.27 ± 1.21	5.41 ± 1.78	0.505	0.091	0.482	0.765
2T2D	4.13 ± 1.32	6.33 ± 3.31	4.19 ± 1.23	5.64 ± 1.86	0.245	0.109	0.624	0.744
4T	4.01 ± 1.23	6.49 ± 3.04	4.12 ± 1.04	5.69 ± 1.80	0.724	0.175	0.401	0.679
CDA								
2T2DR	−1.8 ± 0.88	−0.43 ± 1.32	−1.8 ± 1.44	−0.71 ± 1.39	0.010	0.378	0.922	0.543
2T	−1.8 ± 0.96	−1.30 ± 1.13	−1.3 ± 1.23	−0.60 ± 1.71	2.578	3.291	0.117	0.078
2T2D	−1.4 ± 1.18	−0.70 ± 1.37	−1.7 ± 1.01	−1.25 ± 1.05	0.062	1.458	0.805	0.235
4T	−2.5 ± 1.47	−1.56 ± 0.87	−2.2 ± 1.04	−1.89 ± 1.65	0.324	0.471	0.573	0.497

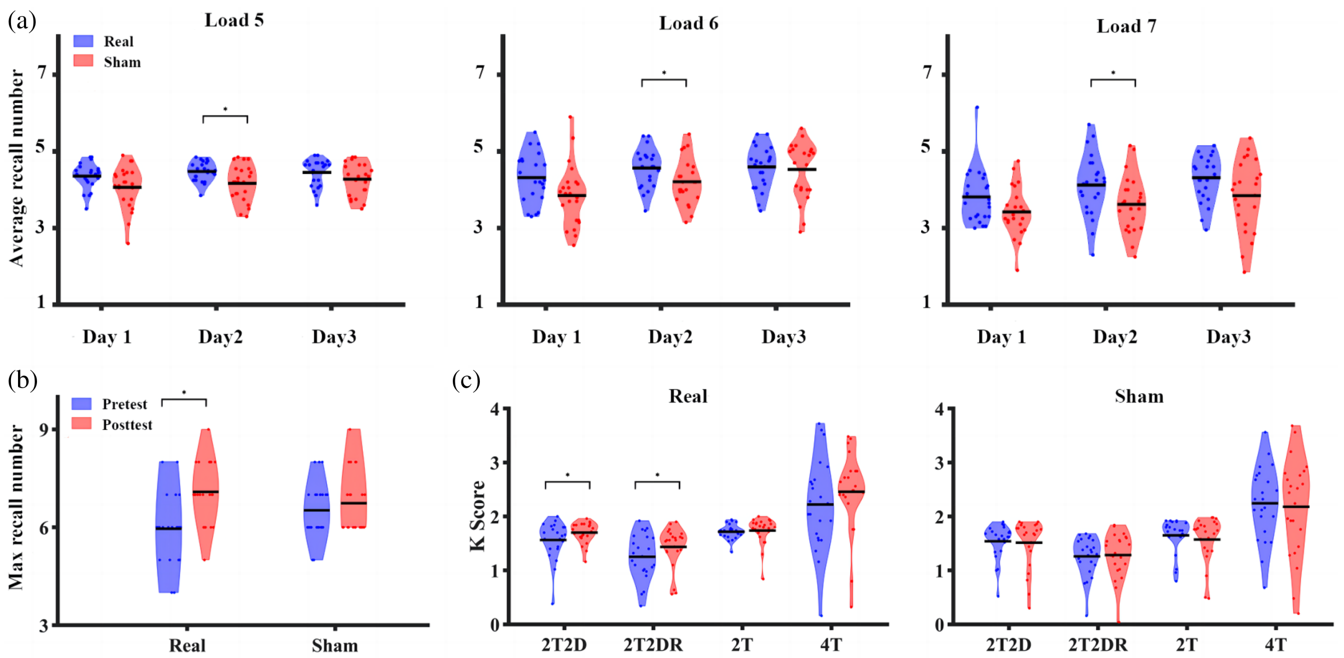

FIGURE 2 Comparisons of behavioral changes between real and sham rTMS. Panel (a) shows average recall number changes at three memory loads across 3 days of rTMS intervention. Panel (b) shows working memory capacity changes as measured by an offline spatial span task. Panel (c) shows K score as measured by a change detection task. Significant differences are indicated by *.

Post hoc analysis showed a significant improvement of the rTMS group for the conditions with distractors (2T2D, $t = 2.711$, $p = .026$; 2T2Dretrocue, $t = 2.733$, $p = .026$) but not for the conditions without distractors (2T, $t = 0.414$, $p = .683$; 4T, $t = 1.777$, $p = .118$) (see Figure 2c). By contrast, the sham group did not show any significant change (all *ps* > .05) (see Figure 2c).

At the neural level, poor EEG data quality (e.g., excessive eye movements or blinking) led to the exclusion of data from six subjects. Within the remaining 40 subjects, 20 received real rTMS whereas the other 20 received sham rTMS. In terms of CDA, three-way repeated measures ANOVA for the two time windows consistently showed significant interaction effects of rTMS × time (300–900 ms, $F_{1,38} = 5.118$; $p = .029$; 1300–1900 ms, $F_{1,38} = 6.908$; $p = .012$). The pattern was very similar to our finding on K score: the real rTMS group showed significant or marginally significant increase in amplitudes of CDAs for the conditions with distractors (2T2D condition: $t = -2.792$, $p = .042$ for 300–900 ms, $t = -2.007$, $p = .059$ for 1300–1900 ms; 2T2Dretrocue condition: $t = -2.051$, $p = .059$ for 300–900 ms, $t = -2.525$, $p = .042$ for 1300–1900 ms), but not for the conditions without distractors (all *ps* > .05). By contrast, the sham rTMS group did not show any significant improvement (all *ps* > .05) (see Figure 3b).

Finally, we explored whether the observed changes (in K score and CDA) could be attributed to parietal alpha activity changes produced by brain stimulation with alpha frequency. Consistent with previous reports, pretest data showed that alpha activity was inhibited (i.e., its power amplitude decreased) during the encoding phase but was enhanced (i.e., its power amplitude increased) during the maintenance phase (see Figure 3c). Repeated measures ANOVA did not show significant changes in alpha activity during the encoding phase (0–300 ms, rTMS × time, $F_{1,38} = 0.377$; $p = .543$). Because brain stimulation with alpha frequency was applied during the maintenance phase, we then conducted repeated measures ANOVA on the same time window as our analysis on CDA. Results showed significant interaction effects of rTMS × time ($F_{1,38} = 5.143$; $p = .029$) for the 1300–1900 ms window, but not for the 300–900 ms window ($F_{1,38} = 0.057$; $p = .813$). Post hoc paired *t* tests further revealed that real rTMS significantly enhanced alpha power for all four conditions (2T2D, $t = 3.617$, $p = .006$; 2T2Dretrocue, $t = 3.135$, $p = .006$; 2T, $t = 2.693$, $p = .014$; 4T, $t = 3.390$, $p = .006$), but sham rTMS group did not change alpha power (all *ps* > .05) (see Figure 3a,c). We also analyzed alpha activity in the hemisphere that is contralateral (task-relevant hemisphere) or ipsilateral (task-irrelevant hemisphere) to the attended visual hemifield. Results showed that alpha activity was enhanced in both hemispheres (see Supplementary Figure S1), suggesting that the enhancement effect of the current rTMS protocol on neural alpha activity was not state-dependent. Finally, we conducted correlation analyses between alpha power changes, CDA changes, and K changes for the conditions with distractors (2T2D, 2T2Dretrocue). There were significant negative correlations between alpha power changes and CDA change ($r = -.543$, $p = .013$) and between CDA change and K change ($r = -.501$, $p = .025$) (see Figure 3c), indicating that the effect of the current rTMS protocol on working memory interference control process may be due to the enhancement of parietal alpha activity during the maintenance phase.

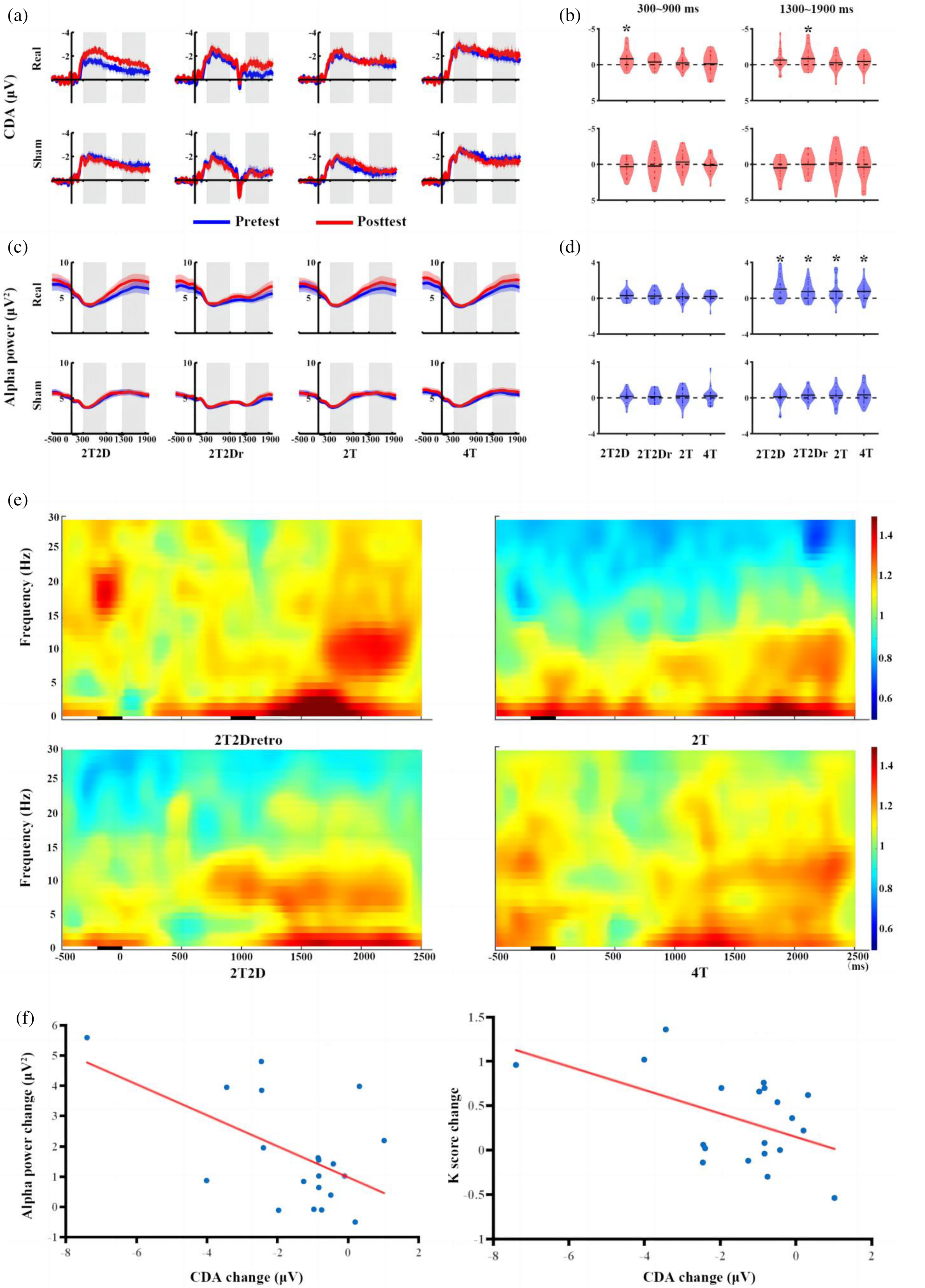

FIGURE 3 Legend on next page.

4 | DISCUSSION

This randomized controlled study demonstrated that repetitive TMS (10 Hz, 3600 pulses in total) at the parietal cortex improved working memory maintenance (based on indices from both the online and the offline spatial span tasks). It also, for the first time, tested the effect of rTMS on the performance on an offline dissimilar task (i.e., the change detection task) and found that it improved interference control but not maintenance. Moreover, the improvement in interference control was at least partly due to rTMS-related enhancement of parietal alpha oscillations. These results show that the combination of cognitive practice and brain stimulation can boost working memory capability.

First, this study found significant time × group interaction effects in the alpha power analysis, which indicated that the current rTMS protocol produced a persistent (about 1 day) effect on alpha activity. This finding is consistent with previous reports of dynamic changes of alpha activity during working memory (Bonnefond & Jensen, 2012; de Vries et al., 2020; Wianda & Ross, 2019). Although a large number of studies (either using rTMS-EEG, Emrich et al., 2017; Hamidi et al., 2009; Johnson et al., 2010; Sauseng et al., 2009; or using tACS-EEG, Helfrich et al., 2014; Vossen et al., 2015) have reported that online brain stimulation with alpha frequency could entrain alpha oscillation, and some studies further showed that this effect could be sustained up to 70 min (Capotosto et al., 2017; Chen et al., 2015; Chung et al., 2018; Grossheinrich et al., 2009; Klimesch et al., 2003; Marshall et al., 2015; Schindler et al., 2008; Thut et al., 2003; Veniero et al., 2011), our study is the first to show a sustained effect over 24 h. A possible reason is that we used a relatively large dose of rTMS (3600 pulses in this study vs. no more than 2000 pulses in previous studies). Our dose was comparable to that used in some studies with offline rTMS (Rossi et al., 2020), that is, rTMS was delivered before, not during, a task. Offline rTMS has been found to generate more sustained effect on neural oscillation (Hallett, 2007; Lefaucheur et al., 2020; Rossi et al., 2020).

Second, the current rTMS protocol produced both online and offline effects on the performance of the spatial span tasks. This was consistent with the alpha inhibition hypothesis, although not Emrich et al.'s (2017) study that reported no effect of brain stimulation with alpha frequency on its online change detection task without interference control burden. According to the alpha inhibition hypothesis about working memory, the power of alpha activity decreases during the encoding phase but increases during the maintenance phase. The decrease in alpha power during the encoding phase has been interpreted as active preparation for the entry of information (Lemm et al., 2009; Wianda & Ross, 2019), while the increase in alpha power during the maintenance phase served as an active inhibition mechanism to prevent the entry of additional information so that only the already encoded information could be maintained within the working memory system (Bonnefond & Jensen, 2012; Händel et al., 2011). Therefore, locking the time of brain simulation to the maintenance phase may be an important reason for the observed effect in the current study. By contrast, when online brain stimulation is delivered continuously during the whole period of the working memory task, it could facilitate alpha activity during the maintenance phase, but it could have damaged alpha activity during the encoding phase and hence offset any benefit from the increased alpha activity during the maintenance phase (Kemmerer et al., 2022). Moreover, Hamidi et al. (2009) found that delivering online TMS with alpha frequency during the recall phase did not improve working memory, perhaps because rTMS disrupts alpha activity during the recall phase. As reported previously, alpha activity during the recall phase decreases rather than increases (Klimesch, 2012).

Third, this study observed significant rTMS effects on the change detection task at both behavioral (K score) and neural (CDA) levels for the conditions with distractors (i.e., 2T2D and 2T2Dretrocue conditions), but not for the conditions without distractors (i.e., 2T and 4T conditions). These results suggest a significant offline effect on interference control but not maintenance of working memory on a dissimilar task. This study further found a significant correlation between rTMS-related alpha power change and CDA change for the conditions with distractors, suggesting that the improvement of interference control may be attributed to alpha oscillation change. Although the two conditions with distractors involved different executive control processes (i.e., the 2T2D condition involved prospective executive control, and the 2T2Dretrocue condition involved retrospective executive control), their performance depended on alpha suppression. As shown in a previous study (Myers et al., 2015) and the current study, alpha activity increases gradually after 500 ms of cues and is greater in the task-irrelevant hemisphere than in the task-relevant hemisphere. It was then possible that the behavioral effects varied between conditions with and without distractors. For the distractor conditions (2T2D, 2T2Dretrocue), the increased alpha activity within the ipsilateral hemisphere suppressed attention to the visual hemifield that was not cued (by the arrow) and the increased alpha activity within the contralateral hemisphere suppressed attention to the distractors that appeared within the visual hemifield being cued, both of

FIGURE 3 Comparisons of neural changes between real and sham rTMS. Panels (a) and (c), respectively, show CDA and alpha power waveforms by task condition (2T2D, 2T2Dretrocue, 2T, 4T) and time (pretest and posttest). The time windows (300–900 ms and 1300–1900 ms during the maintenance period) are shaded. Black rectangular along the X axis indicated the onset and duration of memory array. Panels (b) and (d), respectively, show changes (posttest-pretest) of mean CDA and alpha power within each time window. Significant differences identified by one-sample t tests (compared with zero) are indicated by *. Panel (e) displays the time-frequency map of rTMS-induced power changes (posttest/pretest), with gray rectangles indicating the onset of the cue (−200 to 0 ms) and retrocue (1150–1350 ms). Panel (f) shows the correlations between changes in alpha power and CDA and between changes in CDA and K-score at conditions with distractors (2T2D, 2T2Dretrocue) after real rTMS.

which benefited task performance. For the no-distractor conditions (2T, 4T), although the increased alpha activity within the ipsilateral hemisphere suppressed attention to the visual hemifield that was not cued and benefited task performance, the increased alpha activity within the contralateral hemisphere might have exceeded cognitive requirements. Accordingly, the unnecessary part of the increased alpha activity within the ipsilateral hemisphere further suppressed attention to the visual hemifield being cued, which led to lower task performance. These counteracting effects resulted in little changes in task performance.

Some of our findings warrant a discussion. First, our analysis of the online spatial span task found a significant rTMS effect but no significant rTMS × time interaction effect. In other words, rTMS improved performance on the spatial span task but could not strengthen the effect across the repeated practice. This is likely due to the low practice dose of the spatial span task in this study. Future research is needed to investigate whether rTMS could interact with working memory training to achieve more training effects. Second, the observed rTMS effect of this study cannot be attributed to the effect of repeated practice of the online spatial span task because no significant behavioral and neural changes were observed within the sham rTMS group, which had the same amount of practice on the same task. Third, some of our previous randomized controlled studies about the effect of spatial span training (Zhang et al., 2020) showed that a small dose of practice of the spatial span task did not improve interference control. Our analyses showed a similar pattern of results for CDA and K scores, perhaps due to the close relationship between K score and CDA (for a review, see Luria et al., 2016). Fourth, alpha activity in the hemispheres both contralateral (task-relevant hemisphere) and ipsilateral (task-irrelevant hemisphere) to the attended visual hemifield was enhanced during the maintenance phase of the change detection task. This may be attributed to the fact that the stimuli of the online task were centrally presented. Fifth, we could have asked subjects after the experiment about the type of stimulation they believed they received in order to rule out some potential confounds (such as the placebo effect). However, it is worth mentioning that all participants in this study were naive to rTMS, and we used a between-subjects design (so subjects could not have learned about the differences between rTMS and control during the experiment), which would have helped reduce some confounding effects. Finally, caution is required when interpreting the observed working memory enhancement, as it may be partially attributed to the effect of peripheral nerve stimulation. Further studies should adopt more proactive control methods, such as using alternative stimulation frequencies or targeting other brain regions to verify the specificity of our findings.

In conclusion, this study found that when a large dose of 10 Hz rTMS was delivered during the maintenance phase of a working memory span task, working memory maintenance (based on both online and offline spatial span tasks) and interference control (based on an offline change detection task) can be improved. Future studies may further optimize the rTMS protocol for working memory training.

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CONFLICT OF INTEREST STATEMENT

All authors report no conflicts of interest related to this publication.

DATA AVAILABILITY STATEMENT

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

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