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The effects of rTMS over orbitofrontal cortex on cognitive functions in first-episode schizophrenia

Qiang Hu[1,2,#], Xiong Jiao[1,#], YanLi Ding[1,#], YanYan Wei[1,#], XiaoChen Tang[1], LiHua Xu[1], HuiRu Cui[1], YingYing Tang[1], HaiChun Liu[3], Jin Gao[4], LingYun Zeng[5], ZhengHui Yi[1], ChunBo Li[1], JianHua Chen[1], JiJun Wang[1,6] and TianHong Zhang[1]

[1]Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Neuromodulation Center, Shanghai Engineering Research Center of Intelligent Psychological Evaluation and Intervention, Shanghai Key Laboratory of Psychotic Disorders, Shanghai 200030, PR China; [2]Department of Psychiatry, Wuhu Hospital of Anding Hospital (The Fourth People's Hospital of Wuhu), Wuhu, China; [3]Department of Automation, Shanghai Jiao Tong University, Shanghai 200240, China; [4]Department of Clinical Psychology, Qilu Hospital (Qingdao), Cheeloo College of Medicine, Shandong University, Qingdao, Shandong, China; [5]Department of Psychiatric Rehabilitation, Shenzhen Kangning Hospital, Shen-Zhen, GuangDong, China and [6]Nantong Fourth People's Hospital and Nantong Brain Hospital, NanTong, Jiangsu 226000, China

Abstract

Background. Cognitive impairment in first-episode schizophrenia (FES) is a major contributor to functional decline, but antipsychotics provide limited cognitive improvement, and few repetitive transcranial magnetic stimulation (rTMS) studies have targeted the orbitofrontal cortex (OFC). This study investigated whether right OFC rTMS enhances specific cognitive functions in FES and its relationship with symptom reduction.

Methods. Ninety drug-naive FES patients were enrolled, with 48 receiving active right OFC rTMS and 42 sham stimulation for 20 sessions over 8 weeks, while all patients took olanzapine (10–20 mg/day). Cognitive function was assessed using the Chinese version of the MATRICS Consensus Cognitive Battery (MCCB) at baseline and week 4, and psychotic symptoms were rated with the Positive and Negative Syndrome Scale (PANSS).

Results. Repeated-measures analysis of variance (RMANOVA) demonstrated a significant Time×Group interaction for visuospatial memory (assessed via the Brief Visuospatial Memory Test-Revised, BVMT; $F = 5.079$, $df = 1, 83$, $p = 0.027$, $\eta 2 = 0.058$). Post hoc tests revealed significant BVMT improvement in the active group ($p < 0.001$) but not in the sham group ($p = 0.312$). In the active group, improvements in BVMT and Neuropsychological Assessment Battery (NAB) scores were significantly correlated with lower PANSS total scores after Bonferroni correction.

Conclusions. These findings indicate that right OFC rTMS improves specific cognitive functions in FES, with cognitive benefits associated with symptom alleviation, supporting the right OFC as a promising target for cognitive intervention in FES.

Introduction

Schizophrenia is a common and severe mental disorder characterized by profound disturbances in thinking, perception, emotion, and behavior (Solmi et al., 2023). By the chronic phase of the illness, cognitive impairments emerge as critical drivers of functional decline (Friedman et al., 1999), significantly limiting patients' ability to maintain social relationships, secure employment, and live independently. This underscores the urgency of implementing targeted strategies to address cognitive function during the first episode of schizophrenia (FES) (Mueser et al., 2023), a pivotal window for intervention to prevent long-term disability (Barlati et al., 2012). However, cognitive impairment in FES remains a particularly challenging clinical issue. A systematic review and network meta-analysis (Feber et al., 2025) encompassing 68 studies and over 9,500 participants demonstrated that antipsychotic drugs, as a group, confer only modest and non-specific cognitive benefits relative to placebo – likely attributable to reductions in positive symptoms rather than direct cognitive enhancement – and no single antipsychotic consistently improves cognitive function. This leaves a critical unmet need for targeted and effective cognitive interventions.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique that has shown promise in improving cognitive function in some studies (Barr et al., 2009, 2013). However, prior research has predominantly targeted the dorsolateral prefrontal cortex (DLPFC) (Francis et al., 2019; Wang et al., 2022), with the specific cognitive domains benefiting from such interventions remaining poorly defined, and many studies lacking

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Corresponding authors:
TianHong Zhang, JianHua Chen, and JiJun Wang.
Emails: zhang_tianhong@126.com (TH.Z.); jianhua.chen@smhc.org.cn (JH.C.); jijunwang27@163.com (JJ.W.)

#The author contributed equally and share first authorship.

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the rigor of randomized controlled trial (RCT) designs (Jiang et al., 2019; Tang et al., 2023; Zhang et al., 2019). Clinicians, however, require clearer insights into which specific cognitive functions may be improved by stimulating particular brain regions—a need that holds significant practical value for formulating evidence-based TMS treatment strategies in clinical practice. The orbitofrontal cortex (OFC) has emerged as a crucial target for understanding and potentially improving cognitive function (Costa et al., 2023; Sosa, Buonomano, & Izquierdo, 2021). It plays a pivotal role in creating cognitive maps, which are essential for guiding behavior based on inferred outcomes. For instance, in rodent studies, the OFC has been shown to be involved in forming associations between cues and outcomes, a process fundamental to cognitive function (W. Shi et al., 2023). In humans, its activity is correlated with decision – making processes that rely on mentally simulated outcomes (Stalnaker, Raheja, & Schoenbaum, 2021). Given its extensive connections with limbic and prefrontal regions, the OFC is uniquely positioned to integrate emotional, motivational, and cognitive information (Elorette et al., 2021; Wilson, Takahashi, Schoenbaum, & Niv, 2014).

The right OFC is a critical hub in neural circuits governing cognitive-emotional integration, making its dysfunction integral to schizophrenia pathophysiology (Hiser & Koenigs, 2018). Structural neuroimaging in FES has consistently demonstrated OFC abnormalities that correlate with symptom severity, particularly agitation and cognitive impairment (Kirschner et al., 2021). These structural deficits disrupt the OFC's role in orchestrating reward processing (via cortical–striatal–dopaminergic circuits) and executive functions (e.g. response inhibition and working memory updating), which are core cognitive domains impaired in early schizophrenia (Zhang et al., 2024). Notably, the right lateral OFC sub-region – our target in this study – exhibits heightened functional connectivity with limbic and prefrontal networks in patients, linking its hypoactivity to both negative symptoms (e.g. anhedonia) and cognitive inflexibility (Xu et al., 2017). While most rTMS research has focused on the dorsolateral prefrontal cortex (Zhang et al., 2019), emerging evidence suggests low-frequency (1 Hz) rTMS of the right OFC can modulate these disrupted circuits (Hu et al., 2025). Guided by this framework, we hypothesized that targeting the right lateral OFC would selectively improve cognitive domains reliant on its functional integrity – deficits of which are key drivers of functional decline in FES.

Against this backdrop, the present study, as a secondary analysis of an RCT, aims to explore the effect of rTMS over the right orbitofrontal cortex (OFC-rTMS) on specific cognitive functions (such as visuospatial memory and sustained attention) in patients with FES, and to further analyze the association between changes in cognitive performance and alleviation of psychotic symptoms. The research hypothesis is that, compared to the sham stimulation group, patients in the active group receiving right OFC-rTMS intervention will exhibit more significant improvements in cognitive domains, and that such cognitive improvements will show a stronger association with the reduction of psychotic symptoms. This is intended to verify the specific value of the OFC as a TMS target in improving cognition and clinical symptoms in FES patients.

Methods

Participants and projects

This study is a secondary analysis of a randomized controlled trial (RCT) investigating the effects of rTMS targeting the right OFC in first-episode schizophrenia (FES), with primary trial outcomes reported elsewhere (Hu et al., 2025; Jiao et al., 2024). The present analysis focuses exclusively on the effects of rTMS on cognitive function.

Participants were recruited from the Shanghai Mental Health Center (SMHC) – China's largest mental health service – between December 2020 and February 2022, during which the RCT was conducted. The study protocol was approved by the SMHC Research Ethics Committee in 2017 (No. 2017-24R1) and adhered to the Declaration of Helsinki. All participants provided written informed consent prior to enrollment, and the trial was registered at the Chinese Clinical Trial Register (ChiCTR2000041106) in accordance with CONSORT guidelines. A detailed protocol is available in the Supplementary Material.

A total of 177 FES patients were referred from the inpatient department (Figure 1). Of these, 34 refused research consent, and 11 failed to meet inclusion criteria, leaving 132 patients eligible for enrollment. Randomization was performed using SAS 9.3 to generate a blocked allocation sequence, with an independent staff member (uninvolved in assessment/treatment) assigning 68 patients to the active rTMS group and 64 to the sham group. During the Treatment phase: In the active group, eight failed protocol compliance (5 incomplete sessions, 3 treatment changes), leaving 60; 12 then did not complete cognitive assessments, resulting in 48 for final analysis. In the sham group, 19 failed protocol compliance (9 incomplete sham sessions, 7 treatment changes, 3 consent withdrawals), leaving 45; three did not complete cognitive assessments, resulting in 42 for final analysis. All 90 analyzed patients (48 active, 42 sham) were drug-naive FES cases (age 18–45 years), diagnosed via DSM-IV criteria, and presented with acute psychotic exacerbation at admission.

Prior to rTMS initiation, participants completed a 1-week inpatient screening phase involving clinical evaluations, physical examinations, electrocardiography, and laboratory tests.

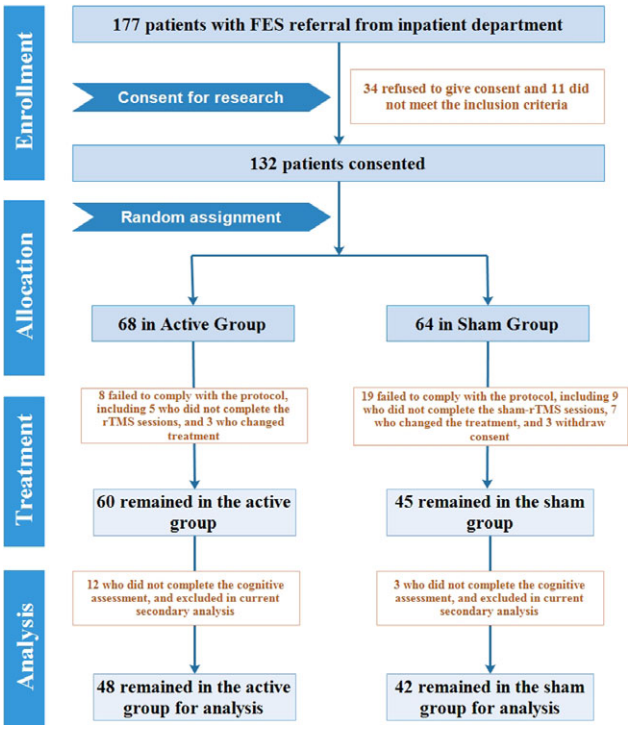


Figure 1. CONSORT flow diagram of participant enrollment, allocation, and analysis.

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Inclusion criteria included: (1) maintenance on a single antipsychotic (olanzapine, 10–20 mg/day) throughout the 8-week treatment period; (2) ability and willingness to complete 20 rTMS sessions. Exclusion criteria included: prior exposure to rTMS, electroconvulsive therapy, or other electromagnetic stimulation; presence of ferromagnetic implants, pacemakers, or a history of neurosurgery, seizures, head trauma, substance abuse/dependence, or suicidal ideation. All rTMS sessions were provided free of charge to participants.

Clinical and cognitive assessments

Psychopathological symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987), a 30-item tool consisting of three subscales: positive (PANSS-P, 7 items: P1–P7), negative (PANSS-N, 7 items: N1–N7), and general psychopathology (PANSS-G, 16 items: G1–G16), with each symptom rated on a 7-point Likert scale (1 = absent to 7 = extreme). Cognitive function was assessed via the Chinese version of the MATRICS Consensus Cognitive Battery (MCCB), administered according to standardized guidelines from the test manual, which included nine subtests consistent with the original version: the Trail Making Test (administered at baseline as Part A and at 4-week follow-up as Part B; TMT), with lower scores indicating better performance – distinct from other subtests, where higher scores reflect stronger performance, Brief Assessment of Cognition in Schizophrenia (BACS) Symbol Coding, Revised Hopkins Verbal Learning Test (HVLT), Wechsler Memory Scale-III Spatial Span (WMS-3 Spatial Span), Neuropsychological Assessment Battery Mazes (NAB Mazes), Revised Brief Visuospatial Memory Test (BVMT), Category Fluency Test (CF), Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT), and Continuous Performance Test-Identical Pairs (CPT-IP), with test–retest reliability ranging from 0.73 to 0.94 in a prior Chinese psychosis sample (Zhang et al., 2024, 2025). All clinical (PANSS) and cognitive (MCCB) assessments were conducted at baseline and week 4 using consistent procedures.

TMS treatment protocol

All rTMS interventions were delivered by trained medical professionals. During each session, participants sat in an ergonomic chair while stimulation was applied to the right OFC – a target validated in earlier studies (Downar, 2019; Feffer et al., 2018; Rolls, 2004) for its role in regulating reward/punishment processing, motivation, decision-making, and goal-directed behaviors, all of which are closely tied to negative symptoms in psychotic disorders (Schoenbaum, Roesch, & Stalnaker, 2006). The AF8 electrode site (per the international 10–20 EEG system) was selected as the stimulation target based on extensive neuroimaging and TMS targeting literature: AF8 is anatomically aligned with the right lateral OFC (rlOFC) with structural MRI co-registration studies confirming that AF8 consistently maps to the rlOFC in adult populations (Feffer et al., 2018), using a MagPro X100 magnetic stimulator (Medtronic Co., Denmark).

Stimulation settings were uniform across all active interventions: a frequency of 1 Hz (Limongi et al., 2021), intensity calibrated to 110% of each participant's motor threshold (MT), and five sessions per week over a 4-week period. Each session consisted of 12 stimulation trains, with 60 pulses per train (administered at 1 Hz) and a 30-second pause between trains. This resulted in 720 pulses per session (with a total treatment duration of 18 minutes) and 14,400 pulses over 20 consecutive treatment days. The 30-second inter-train interval was chosen to balance safety and effectiveness: while low-frequency, high-intensity stimulation has demonstrated clinical benefits with a reduced risk of seizures (Klein et al., 1999), limited data exist on the safety of continuous (interval-free) train delivery, making spaced trains a more prudent approach.

Participants in the sham group underwent an identical procedural sequence but with a placebo coil that did not produce a magnetic field. To maintain blinding, the placebo coil matched the active coil in appearance and emitted a 'click' sound indistinguishable from the active device – preventing participants from identifying their treatment group. The placebo coil was also identical in weight to the active coil, eliminating tactile cues that could unblind rTMS technicians during coil handling and positioning. Additionally, two separate teams of blinded personnel were involved: one team of blinded evaluators conducted clinical assessments to avoid outcome bias, while another team of blinded trained physicians managed rTMS administration, including motor threshold determination and group allocation (active versus sham) based on a random number table. Physicians were instructed to refrain from non-treatment-related conversations with participants during sessions to preserve the integrity of the blinding process.

For safety monitoring, a standardized checklist was developed to assess rTMS-related adverse events. Following each session, participants were evaluated for seven potential side effects, each rated on a 0–9 scale: headache, fatigue, dizziness, ocular/nasal discomfort, temporomandibular joint or dental discomfort, facial discomfort, and drowsiness.

Data analysis

For comparisons of demographic characteristics, clinical symptoms, and cognitive performances at baseline and 4-week follow-up between the active and sham groups, independent t-tests were used for continuous variables and chi-square (χ^2) tests for categorical variables. Repeated-measures analysis of variance (RMANOVA) was conducted to examine the effects of time (baseline versus 4-week), group (active versus sham), and their interaction (Time × Group) on cognitive variables, with partial eta-squared (η^2) reported as effect sizes (small: $\eta^2 = 0.01$, medium: $\eta^2 = 0.06$, large: $\eta^2 = 0.14$). For cognitive domains with a significant Time×Group interaction in RMANOVA, post hoc paired t-tests were applied to analyze within-group changes in cognitive test scores from baseline to 4-week follow-up. Pearson's correlation coefficients were used to explore relationships between changes (Δ, baseline minus 4-week) in PANSS scores (total, P, N, G subscales) and changes in cognitive test scores, analyzed for the total sample, active group, and sham group separately. Statistical significance was set at $p < 0.05$, and all analyses accounted for varying sample sizes across cognitive tests due to data availability.

Results

Demographic, clinical, and cognitive characteristics

At baseline, the active rTMS group ($n = 48$) and sham group ($n = 42$) were well-matched in demographics, clinical characteristics (including PANSS scores), and neurocognitive performances (all $p > 0.05$). After 4 weeks, the active group exhibited significantly lower PANSS total scores (58.9 ± 10.6 versus 67.3 ± 15.4, $t = -3.058$, $df = 88$, $p = 0.003$), PANSS-N (16.2 ± 4.2 versus 19.0 ± 6.4, $t = -2.554$, $df = 88$, $p = 0.012$), and PANSS-G scores (30.2 ± 5.0 versus 34.2 ± 6.2, $t = -3.371$, $df = 88$, $p = 0.001$) relative to the sham group, with a trend toward significance in PANSS-P ($p = 0.098$).

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Table 1. Demographic, clinical characteristics, and neurocognitive performances at baseline and after 4 weeks of orbitofrontal cortex-repetitive transcranial magnetic stimulation (OFC-rTMS): group comparisons between active and sham groups

	Baseline			4-week		
			Comparisons			Comparisons
Variables [Mean (SD)]	Active	Sham	$t/\chi^2(df)$, p, Cohen's d	Active	Sham	$t(df)$, p, Cohen's d
Cases [n]	48	42	–	48	42	–
Sex (%)	27 (56.3%)	21 (43.8%)	$\chi^2(1) = 1.087$, $p = 0.297$	–	–	–
Age (year)	27.1 (8.1)	26.4 (7.8)	$t(88) = 0.417$, $p = 0.678$, $d = 0.09$	–	–	–
Education (year)	11.5 (3.9)	10.6 (3.6)	$t(88) = 1.109$, $p = 0.270$, $d = 0.24$	–	–	–
PANSS-total	81.7 (11.2)	81.0 (9.9)	$t(88) = 0.316$, $p = 0.753$, $d = 0.07$	58.9(10.6)	67.3(15.4)	$t(88) = -3.058$, $p = 0.003$, $d = 0.65$
PANSS-P	20.1 (4.0)	19.8 (4.1)	$t(88) = 0.428$, $p = 0.670$, $d = 0.09$	12.5(3.9)	14.0(5.0)	$t(88) = -1.674$, $p = 0.098$, $d = 0.35$
PANSS-N	22.2 (5.5)	22.7 (5.8)	$t(88) = -0.401$, $p = 0.689$, $d = 0.09$	16.2(4.2)	19.0(6.4)	$t(88) = -2.554$, $p = 0.012$, $d = 0.54$
PANSS-G	39.4 (6.1)	38.6 (4.6)	$t(88) = 0.720$, $p = 0.473$, $d = 0.15$	30.2(5.0)	34.2(6.2)	$t(88) = -3.371$, $p = 0.001$, $d = 0.71$
DUP (Month)	13.8 (21.6)	17.3 (18.3)	$t(88) = -0.836$, $p = 0.406$, $d = 0.18$	–	–	–
OLZ-Dosage (mg)	–	–	–	16.5(3.7)	16.9(3.8)	$t(88) = -0.562$, $p = 0.576$, $d = 0.12$
MT	41.0 (6.4)	39.4 (5.4)	$t(88) = 1.326$, $p = 0.188$, $d = 0.28$	–	–	–
Cognitive performances						
TMT	56.6 (38.9)	57.5 (33.6)	$t(82) = -0.116$, $p = 0.908$, $d = 0.03$	40.6 (17.9)	44.9 (32.4)	$t(82) = -0.752$, $p = 0.454$, $d = 0.16$
BACS	44.7 (10.7)	42.8 (12.3)	$t(83) = 0.804$, $p = 0.424$, $d = 0.17$	47.9 (10.2)	44.0 (11.9)	$t(83) = 1.625$, $p = 0.108$, $d = 0.35$
HVLT	22.4 (6.5)	21.9 (5.7)	$t(83) = 0.367$, $p = 0.715$, $d = 0.08$	23.0 (5.9)	21.0 (5.3)	$t(83) = 1.629$, $p = 0.107$, $d = 0.35$
WMS–3	14.7 (3.9)	14.9 (4.2)	$t(81) = -0.291$, $p = 0.772$, $d = 0.06$	16.3 (3.6)	15.8 (4.1)	$t(81) = 0.541$, $p = 0.590$, $d = 0.12$
NAB	10.8 (6.6)	11.1 (6.9)	$t(83) = -0.214$, $p = 0.831$, $d = 0.05$	13.3 (6.3)	13.2 (6.4)	$t(83) = 0.093$, $p = 0.926$, $d = 0.02$
BVMT	19.2 (9.1)	19.7 (7.7)	$t(83) = -0.318$, $p = 0.751$, $d = 0.07$	22.9 (7.7)	20.5 (8.1)	$t(83) = 1.430$, $p = 0.156$, $d = 0.31$
CF	19.9 (4.7)	17.8 (5.9)	$t(82) = 1.837$, $p = 0.070$, $d = 0.40$	19.8 (5.3)	18.0 (5.6)	$t(82) = 1.486$, $p = 0.141$, $d = 0.32$
MSCEIT	80.6 (8.3)	79.1 (7.4)	$t(70) = 0.772$, $p = 0.443$, $d = 0.19$	80.7 (9.3)	78.8 (8.5)	$t(70) = 0.909$, $p = 0.367$, $d = 0.22$
CPT-IP	1.9 (0.7)	1.7 (0.8)	$t(75) = 1.167$, $p = 0.247$, $d = 0.27$	2.1 (0.8)	1.8 (0.8)	$t(75) = 2.069$, $p = 0.042$, $d = 0.47$

Note: Independent t-tests were used for continuous variables, and chi-square (χ^2) tests were used for categorical variables. Cohen's d was calculated using the pooled standard deviation formula for independent samples. Cohen's d interpretation: 0.2 = small effect, 0.5 = medium effect, 0.8 = large effect. BACS, Brief Assessment of Cognition in Schizophrenia Symbol Coding; BVMT , Brief Visuospatial Memory Test-Revised; CPT-IP, Continuous Performance Test-Identical Pairs; CF, Category Fluency; DF, Degrees of Freedom; DUP, Duration of Untreated Psychosis; HVLT, Hopkins Verbal Learning Test-Revised; MSCEIT, Mayer–Salovey–Caruso Emotional Intelligence Test; MT, Motor Threshold; NAB, Neuropsychological Assessment Battery; OLZ-Dosage, Olanzapine Dosage; PANSS, Positive and Negative Syndrome Scale; PANSS-G, PANSS General Psychopathology Subscale; PANSS-N, PANSS Negative Symptom Subscale; PANSS-P, PANSS Positive Symptom Subscale; TMT, Trail Making Test; WMS-3, Wechsler Memory Scale-Third Edition.

Olanzapine dosage did not differ between groups ($p = 0.576$). In neurocognition, only CPT-IP showed a significant improvement in the active group (2.1 ± 0.8 versus 1.8 ± 0.8, $t = 2.069$, $df = 75$, $p = 0.042$), while other measures had no significant group differences (all $p > 0.05$) (Table 1).

Repeated-measures analysis of cognitive function changes over time

To evaluate treatment-specific cognitive effects (i.e. whether active rTMS produced changes distinct from sham), we conducted a 2 (Group: active versus sham) × 2 (Time: baseline versus Week 4) RMANOVA for each cognitive variable – with the Group × Time interaction as the critical outcome to identify treatment-specific benefits (Table 2).

Significant time effects (collapsed across groups) were observed for TMT, BACS, WMS-3, NAB, BVMT, and CPT-IP (all $p < 0.05$), indicating overall cognitive improvement over 4 weeks in both groups (likely reflecting non-specific effects such as practice, symptom reduction from olanzapine, or natural recovery). A significant Group effect was only observed for CPT-IP ($F = 4.005$, $df = 1, 75$, $p = 0.049$, $\eta^2 = 0.051$), reflecting a general between-group difference in sustained attention independent of time. Critically, only BVMT (visuospatial memory) exhibited a significant Group × Time interaction ($F = 5.079$, $df = 1, 83$, $p = 0.027$, $\eta^2 = 0.058$). No other cognitive measures (TMT, BACS, WMS-3, NAB, CF, MSCEIT, and CPT-IP) showed significant Group × Time interactions (all $p > 0.05$). Figure 2 visually depicts these changes, with different panels (A-I) corresponding to each cognitive test, showing the score trajectories of the active (red) and sham (blue) groups from baseline to 4-week follow-up, aligning with the RMANOVA results in Table 2.

Post hoc paired comparisons of active and sham groups

Figure 3 illustrates post hoc paired analyses of BVMT scores for active (left panel) and sham (right panel) groups at baseline and 4-week follow-up. The active group demonstrated significant gains in the BVMT ($t = 3.631$, $df = 43$, $p = 0.0007$), with the sham group yielding non-significant results (ns).

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Table 2. Repeated – measures analysis of variance (RMANOVA) on changes in cognitive variable scores

	N		Time			Group			Time × Group		
Cognitive variables	Active	Sham	*F (df1, df2)*	*p*	η^2	*F (df1, df2)*	*p*	η^2	*F (df1, df2)*	*p*	η^2
TMT	43	41	**23.184** (1, 82)	**<0.001**	**0.220**	0.182 (1, 82)	0.671	0.002	0.272 (1, 82)	0.603	0.003
BACS	44	41	**8.461** (1, 83)	**0.005**	**0.093**	1.927 (1, 83)	0.169	0.023	0.723 (1, 83)	0.398	0.009
HVLT	43	42	0.148 (1, 83)	0.701	0.002	1.172 (1, 83)	0.282	0.014	1.172 (1, 83)	0.282	0.014
WMS–3	43	40	**8.361** (1, 80)	**0.005**	**0.094**	0.009 (1, 80)	0.926	0.000	1.044 (1, 80)	0.310	0.013
NAB	43	42	**20.753** (1, 83)	**<0.001**	**0.200**	0.208 (1, 83)	0.650	0.002	0.397 (1, 83)	0.531	0.005
BVMT	44	41	**9.134** (1, 83)	**0.003**	**0.099**	0.439 (1, 83)	0.509	0.005	**5.079** (1, 83)	**0.027**	**0.058**
CF	42	42	0.061 (1, 82)	0.806	0.001	3.040 (1, 82)	0.095	0.036	0.039 (1, 82)	0.844	0.000
MSCEIT	35	36	0.543 (1, 69)	0.464	0.008	0.759 (1, 69)	0.387	0.011	0.136 (1, 69)	0.714	0.002
CPT-IP	39	38	**6.719** (1, 75)	**0.011**	**0.082**	**4.005** (1, 75)	**0.049**	**0.051**	2.110 (1, 75)	0.150	0.027

Note: This table presents *F*-values, *p*-values, and partial eta-squared (η^2) effect sizes for within-subjects (Time, Time × Group) and between-subjects (Group) factors. df1 = between-subjects degrees of freedom, df2 = within-subjects error degrees of freedom. Analyses compare baseline and 4-week scores between active and sham groups. Bold values indicate statistical significance ($p < 0.05$). Effect size benchmarks: $\eta^2 = 0.01$ (small), 0.06 (medium), 0.14 (large). Sample sizes (*N*) vary by test due to data availability. BACS, Brief Assessment of Cognition in Schizophrenia Symbol Coding; BVMT , Brief Visuospatial Memory Test-Revised; CPT-IP, Continuous Performance Test-Identical Pairs; CF, Category Fluency; HVLT, Hopkins Verbal Learning Test-Revised; MSCEIT, Mayer–Salovey–Caruso Emotional Intelligence Test; NAB, Neuropsychological Assessment Battery; TMT, Trail Making Test; WMS-3, Wechsler Memory Scale-Third Edition.

Correlation analysis between changes in PANSS scores and cognitive performances

Table 3 presents correlation analyses (Pearson's *r*) between changes in PANSS scores (total, PANSS-P, PANSS-N, and PANSS-G) and changes in cognitive test scores (baseline to 4-week), conducted separately for three cohorts: the total sample (ALL), active rTMS group, and sham group. To control family-wise error rate (FWER) for each subgroup (independent analytical family), Bonferroni correction was applied per subgroup ($\alpha = 0.05/9 \approx 0.0056$, accounting for 9 cognitive tasks per subgroup). Significant negative correlations were observed: BACS, WMS-3, and NAB change correlated with PANSS-total change; NAB change correlated with PANSS-P change; WMS-3 change correlated with PANSS-N change; NAB change correlated with PANSS-G change in the total sample. In subgroup analyses, the active group showed statistically significant associations: NAB change correlated with PANSS-total ($r = -0.489$, $df = 41$, $p = 0.001$) and PANSS-G ($r = -0.440$, $df = 41$, $p = 0.003$) changes; BVMT change correlated with PANSS-total ($r = 0.440$, $df = 42$, $p = 0.003$) and PANSS-G ($r = 0.473$, $df = 42$, $p = 0.001$) changes; WMS-3 change correlated with PANSS-N ($r = -0.320$, $df = 42$, $p = 0.036$) change. Most correlations in the sham group were non-significant.

Discussion

This RCT offers several key strengths, including its rigorous study design, the innovative selection of the OFC as a stimulation target, and the use of a medication-naive FES sample (with no prior physical or pharmacologic treatment history), which minimizes potential confounding effects. The primary RMANOVA analysis revealed that right OFC-rTMS exerts a domain-specific cognitive effect: only BVMT (visuospatial memory) showed a significant Time × Group interaction, indicating that this cognitive domain benefited specifically from the intervention. Post hoc paired t-tests further confirmed this specificity: the active group exhibited a significant within-group improvement in BVMT, while the sham group showed no significant change.

The significant Time × Group interaction for BVMT (visuospatial memory) likely stems from the OFC's role in integrating visuospatial information with contextual and mnemonic processes. Zhu et al. (2020) identified that an impaired parahippocampal gyrus-OFC circuit underlies visuospatial memory deficits in Alzheimer's disease, highlighting this circuit's essential role in visuospatial memory (Zhu et al., 2020). Han et al. (2023) identified a functional OFC-hippocampal pathway whose potentiation mediates therapeutic effects, and the OFC is also connected to the posterior parietal cortex, forming a network critical for consolidating visual-spatial memories (Han et al., 2023). Our findings suggest right OFC-rTMS may normalize activity in this OFC-hippocampal-parietal network: by modulating the OFC's ability to encode contextual cues tied to visuospatial stimuli, the intervention could enhance the consolidation of spatial memories – consistent with the BVMT's focus on recalling visual layouts over time. Fleming et al. (1997) further demonstrated that patients with schizophrenia exhibit marked deficits in visuospatial memory tasks despite intact basic perceptual abilities, pointing to impairments in neural networks involving prefrontal regions (Fleming et al., 1997). Notably, the specificity of our BVMT effect aligns with prior work showing the right lateral OFC is uniquely involved in linking spatial context to memory retrieval – unlike other prefrontal regions (e.g. DLPFC) that support more domain-general executive functions.

The significant Group main effect for CPT-IP (sustained attention) reflects a general between-group difference in performance (collapsed across time) but does not indicate a treatment effect of OFC-rTMS. Critically, the absence of a Time × Group interaction for CPT-IP confirms that the active intervention did not modify sustained attention over time – any baseline-to-4-week changes in CPT-IP were similar between groups, and the main effect likely reflects pre-existing or non-intervention-related differences in attention between cohorts. The OFC is part of the frontoparietal attention network (Ptak, 2012), regulating the allocation of cognitive resources to sustained tasks by inhibiting distractors and reinforcing task-relevant goals (Miller & Cohen, 2001). He et al. (2013) found that in first-episode treatment-naive schizophrenia patients, aberrant intrinsic activity in the OFC correlates with neurocognitive deficits, and increased default mode network connectivity in the left insula – linked to the OFC – was specifically associated with deficits in sustained attention (He et al., 2013). While these studies highlight the OFC's relevance to sustained

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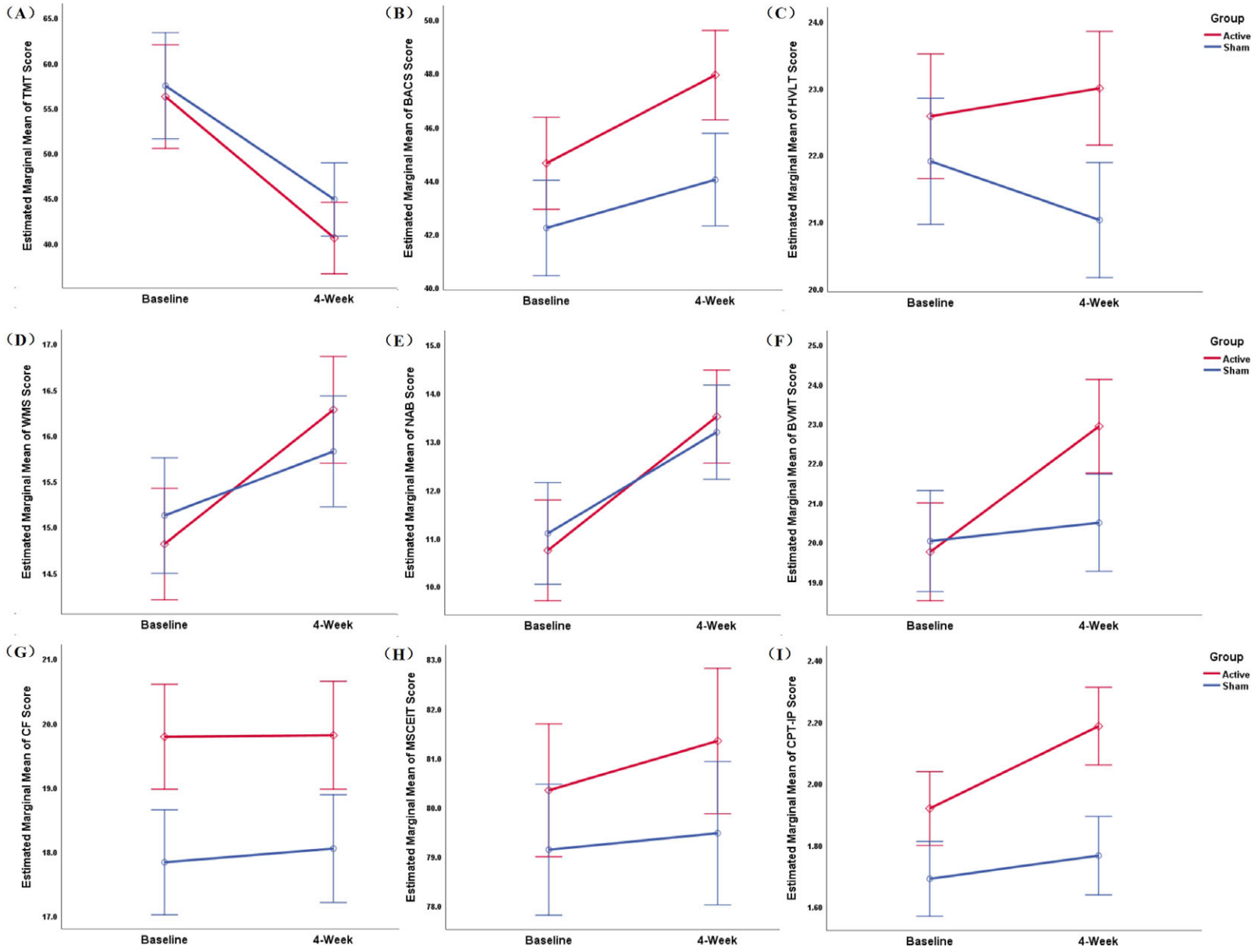


Figure 2. Trajectories of cognitive test score changes in active and sham groups. Each panel (a–i) corresponds to a cognitive test. Red lines represent the active group, blue lines the sham group, showing score changes from baseline to 4-week follow-up. Vertical error bars represent standard error (SE) of the mean, indicating the precision of group-level estimates. *Note*: BACS, Brief Assessment of Cognition in Schizophrenia Symbol Coding; BVMT, Brief Visuospatial Memory Test-Revised; CPT-IP, Continuous Performance Test-Identical Pairs; CF, Category Fluency; HVLT, Hopkins Verbal Learning Test-Revised; MSCEIT, Mayer–Salovey–Caruso Emotional Intelligence Test; NAB, Neuropsychological Assessment Battery; TMT, Trail Making Test; WMS-3, Wechsler Memory Scale-Third Edition.

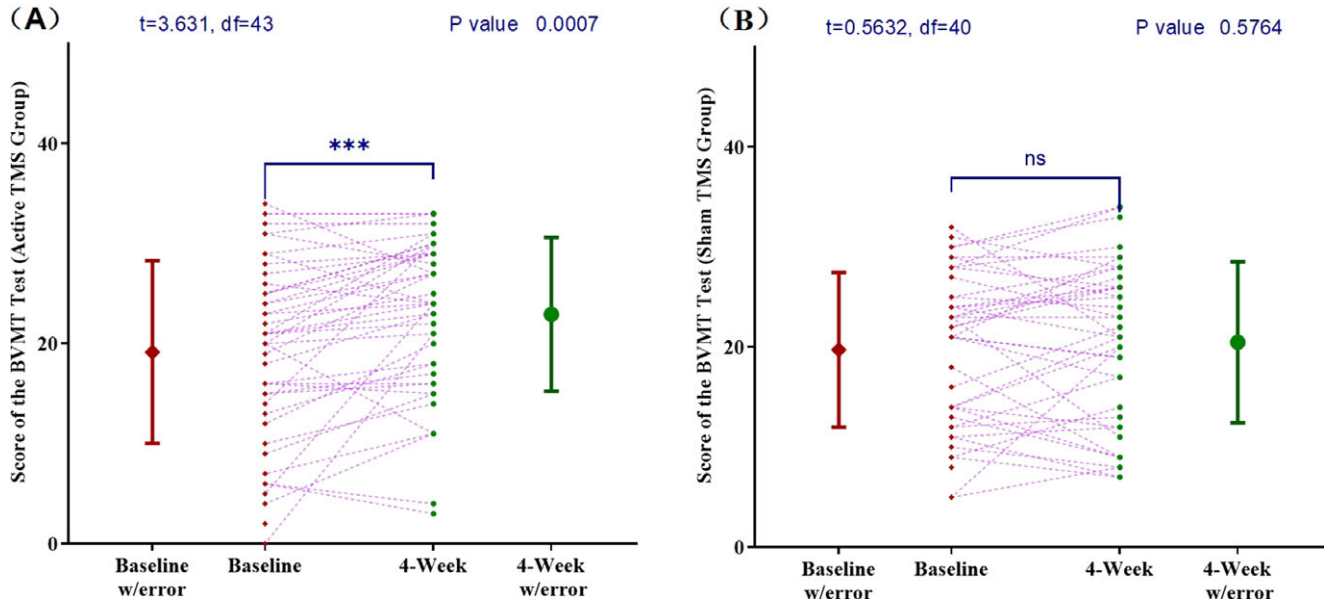


Figure 3. Post hoc analysis of BVMT scores (visuospatial memory) following significant Time × Group interaction in RMANOVA in active and sham groups. Panels (a,b) display baseline- to 4-week score trajectories for the active (red) and sham (green) groups. Paired scores are linked by lines, and error bars show data spread. t-values, *df*, and *p*-values indicate significance: ***** for significant effects, *ns* for no effect. *Note*: BVMT, Brief Visuospatial Memory Test-Revised.

Table 3. Correlation analysis between ΔPANSS scores and ΔCognitive test scores (baseline to 4-week)

Cognitive variables		Δ PANSS-total			Δ PANSS-P			Δ PANSS-N			Δ PANSS-G		
		ALL	Active	Sham	ALL	Active	Sham	ALL	Active	Sham	ALL	Active	Sham
ΔTMT	*r*	0.015	−0.062	0.072	−0.045	−0.092	−0.008	−0.029	−0.143	0.107	0.088	0.071	0.075
	p	0.895	0.693	0.655	0.685	0.556	0.959	0.795	0.361	0.507	0.428	0.652	0.643
	N	84	43	41	84	43	41	84	43	41	84	43	41
ΔBACS	*r*	−.250*	−0.248	−0.218	−0.209	−0.179	−0.214	−0.193	−0.168	−0.182	−0.171	−0.182	−0.110
	p	0.021	0.104	0.170	0.055	0.245	0.179	0.077	0.277	0.254	0.117	0.237	0.493
	N	85	44	41	85	44	41	85	44	41	85	44	41
ΔHVLT	*r*	−0.200	−0.212	−0.126	−0.198	−0.300	−0.051	−0.156	−0.154	−0.104	−0.112	−0.023	−0.131
	p	0.066	0.172	0.428	0.070	0.051	0.748	0.153	0.324	0.512	0.306	0.886	0.407
	N	85	43	42	85	43	42	85	43	42	85	43	42
ΔWMS–3	*r*	−.244*	−0.262	−0.170	−0.084	−0.159	0.053	−.281**	−.320*	−0.188	−0.200	−0.113	−0.253
	p	0.026	0.090	0.295	0.450	0.309	0.748	0.010	0.036	0.244	0.070	0.471	0.116
	N	83	43	40	83	43	40	83	43	40	83	43	40
ΔNAB	*r*	−.310**	−.489**	−0.122	−.230*	−.373*	−0.064	−0.150	−0.189	−0.079	−.301**	−.440**	−0.132
	p	0.004	0.001	0.441	0.034	0.014	0.689	0.170	0.224	0.618	0.005	0.003	0.404
	N	85	43	42	85	43	42	85	43	42	85	43	42
ΔBVMT	*r*	0.098	.440**	−0.046	0.180	0.287	0.171	−0.048	0.130	−0.113	0.074	.473**	−0.166
	p	0.375	0.003	0.777	0.100	0.059	0.284	0.663	0.402	0.484	0.499	0.001	0.299
	N	85	44	41	85	44	41	85	44	41	85	44	41
ΔCF	*r*	−0.133	−0.163	−0.142	−0.201	−0.242	−0.177	0.028	0.021	0.025	−0.112	−0.110	−0.151
	p	0.229	0.304	0.369	0.067	0.122	0.263	0.802	0.897	0.876	0.312	0.487	0.340
	N	84	42	42	84	42	42	84	42	42	84	42	42

(*Continued*)

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Table 3. (*Continued*)

Cognitive variables		Δ PANSS-total			Δ PANSS-P			Δ PANSS-N			Δ PANSS-G		
		ALL	Active	Sham	ALL	Active	Sham	ALL	Active	Sham	ALL	Active	Sham
ΔMSCEIT	*r*	0.113	0.094	0.195	0.047	−0.093	0.200	0.021	0.035	0.041	0.164	0.202	0.183
	p	0.348	0.593	0.254	0.697	0.596	0.243	0.860	0.840	0.812	0.172	0.246	0.286
	N	71	35	36	71	35	36	71	35	36	71	35	36
ΔCPT-IP	*r*	−0.105	0.048	−0.100	0.060	0.130	0.080	−0.218	−0.101	−0.244	−0.087	0.060	−0.086
	p	0.364	0.770	0.551	0.606	0.430	0.634	0.057	0.542	0.140	0.452	0.715	0.607
	N	77	39	38	77	39	38	77	39	38	77	39	38

Note: 'Δ' denotes the difference between 4-week and baseline scores (4-week–baseline). Cognitive tests: TMT (Trail Making Test), BACS (Brief Assessment of Cognition in Schizophrenia), HVLT (Hopkins Verbal Learning Test), WMS-3 (Wechsler Memory Scale-Third Edition), NAB (Neuropsychological Assessment Battery), BVMT (Brief Visuospatial Memory Test), CF (Category Fluency), MSCEIT (Mayer–Salovey–Caruso Emotional Intelligence Test), CPT-IP (Continuous Performance Test-Identical Pairs). PANSS subscales: total (PANSS-total), positive (PANSS-P), negative (PANSS-N), general psychopathology (PANSS-G). Significance levels: uncorrected $p < 0.05$, uncorrected $p < 0.01$. To account for multiple comparisons (9 cognitive measures), Bonferroni correction was applied per subgroup ($\alpha = 0.05/9 \approx 0.0056$) to control FWER for nine cognitive tasks per subgroup. After correction, significant correlations include: ΔNAB with ΔPANSS-total (active group, $p = 0.001$), ΔNAB with ΔPANSS-G (active group, $p = 0.003$), and ΔBVMT with ΔPANSS-G (active group, $p = 0.001$). Sample sizes (N) vary by test due to data availability.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

attention, our RMANOVA results confirm that right OFC-rTMS did not exert a measurable effect on this domain in the current study.

Within the active group, cognitive improvements were significantly correlated with reductions in total psychotic symptoms and general psychopathology, after controlling for multiple comparisons. In contrast, no significant correlations between cognitive changes and symptom reductions were observed in the sham group (all $p > 0.0056$). This pattern is likely attributable to the OFC's role as a critical hub for integrating emotional, motivational, and cognitive processes (Grossberg, 2018), wherein rTMS-induced modulation may concurrently enhance both domains. The OFC is densely connected to limbic regions (e.g. amygdala, hippocampus) (Fraser & Janak, 2023) involved in symptom expression and prefrontal regions supporting cognitive function, forming a network where improvements in one domain (e.g. reduced negative or general psychopathology symptoms) may facilitate gains in the other (e.g. memory, attention). In the active group, OFC-TMS likely strengthened this network's coherence (Daly, Williams, & Nasuto, 2024): alleviating symptoms by normalizing hyperactive emotional responses and concurrently enhancing cognitive efficiency by improving information integration – creating a reciprocal relationship between symptom relief and cognitive gains. In contrast, the sham group lacked such targeted neuromodulation, leaving the dysfunctional network unaltered and thus failing to establish meaningful correlations between symptom and cognitive changes.

This study has several limitations that should be noted. First, although there was no statistically significant difference in olanzapine dosage between the two groups, antipsychotic medication remains a potential confounding factor, as it may independently influence both psychotic symptoms and cognitive function, complicating the interpretation of rTMS-specific effects. Olanzapine has been shown to exert modest effects on certain cognitive domains in FES patients, primarily via its modulation of dopaminergic and serotonergic pathways. This raises the possibility that the cognitive improvements observed in both groups may partially reflect non-specific effects of olanzapine rather than rTMS. Nevertheless, the inability to isolate rTMS effects from olanzapine's cognitive impacts limits our ability to definitively attribute all observed gains to OFC neuromodulation, highlighting the need for future studies (e.g. medication-free cohorts or randomized controlled trials of rTMS as monotherapy) to clarify this distinction. Second, the sample sizes of the active and sham groups were unequal (48 versus 42), primarily due to a higher number of dropouts in the sham group, which may introduce bias and reduce the statistical power to detect group differences. Third, the overall sample size was relatively limited, limiting the generalizability of the findings to broader FES populations. Fourth, while participants were blinded to treatment assignment, the effectiveness of the blinding was not formally assessed or confirmed, leaving open the possibility that unblinding could have influenced outcomes such as symptom reporting or cognitive test performance. Fifth, the study only assessed cognitive function at baseline and 4 weeks post-intervention, without long-term follow-up (e.g. 3, 6, or 12 months). This precludes the evaluation of the stability of observed cognitive improvements (e.g. BVMT gains) and the determination of whether sustained benefits necessitate maintenance rTMS sessions – a critical consideration for clinical translation.

Conclusions

Right OFC-rTMS demonstrates potential for improving a specific cognitive domain (visuospatial memory) in FES patients. Within the active group, cognitive gains were significantly correlated with reductions in psychotic symptoms, whereas no such significant correlations were observed in the sham group. These findings highlight the OFC as a viable target for neuromodulatory interventions, though further studies with larger samples and optimized designs are needed to confirm and extend these results.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0033291726103912.

Data availability statement. The datasets generated and/or analyzed during the current study are available from the corresponding author on request.

Author contribution. T.Z., Q.H., X.J., Y.D., and J.W. conceptualized the study, wrote the first draft of the manuscript, and conducted the statistical analyses. L.X., J.G., H.C., X.T., and Y.W. interviewed participants and collected and organized the primary data. Y.Z., Z.Y., C.L., H.L., and Y.T. managed the literature searches, statistical analyses, and edited the manuscript. T.Z., J.C., and J.W. designed the study and provided supervision in the implementation of the study. All authors have approved the final manuscript.

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Competing interests. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical standard. This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was granted by the Research Ethics Committee at the Shanghai Mental Health Center. Participants gave written informed consent at the time of the recruitment stage.

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