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CLINICAL TRIAL REPORT

# Efficacy of Cortical-Hippocampal Target Intermittent Theta Burst Stimulation (iTBS) on Associative Memory of Schizophrenia: A Double-Blind, Randomized Sham-Controlled Trial

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**Objective:** The objective of our study was to evaluate whether intermittent theta burst stimulation(iTBS) applied to the regions with the strongest cortico-hippocampal connectivity within the lateral parietal cortical (LPC) or dorsolateral prefrontal cortical (DLPFC) areas in individuals with schizophrenia could enhance associative memory.

**Methods:** We randomized 96 participants with schizophrenia to receive either active iTBS applied to the right DLPFC, left LPC or sham iTBS for 20 days. Clinical and cognitive assessments were performed at baseline and at the end of treatment. The primary outcome was change in associative memory. The secondary outcome was change in other cognitive functions and psychiatric symptoms.

**Results:** In comparison to the sham group, iTBS targeting the right DLPFC or left LPC in schizophrenia did not yield significant improvements in auditory-auditory associative memory (F=1.27, p=0.294), auditory-visual associative memory (F=0.49, p=0.617), or visual-visual associative memory (F=1.094, p=0.347). Furthermore, after adjusting for variables such as education, disease duration, and negative symptoms, no significant changes were observed in any of these three memory domains.

**Conclusion:** Although our study suggests that iTBS applied to the cortical-hippocampal did not lead to a significant change in associative memory. However, further investigation combining hippocampal-targeted iTBS with functional magnetic resonance imaging (fMRI) is warranted to elucidate the regulatory effects of iTBS on hippocampal function.

**Trial Registration:** clinicaltrials.gov NCT03608462.

**Keywords:** theta burst stimulation, associative memory, schizophrenia, cortical-hippocampal network

## Introduction

Schizophrenia is a severe mental illness characterized by a combination of positive symptoms, negative symptoms and cognitive impairment.[1] Among them, cognitive deficits are an important factor affecting the functional prognosis of schizophrenia.[2–4] However, existing interventions such as antipsychotic medications,[5,6] pro-cognitive medications,[7] or cognitive remediation therapy[8,9] are ineffective or only marginally effective in treating cognitive deficits.

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Episodic memory (EM) deficits are a core cognitive deficit symptom in schizophrenia.[2,10,11] EM entails not only the storage and retrieval of images, sounds, locations, temporal information, and contextual details of events or situations but also the integration of these internally related situational segments into a cohesive memory representation.[12] Associative memory, which consolidates the details of various attributes into a unified representation, constitutes a fundamental component of episodic memory.The hippocampus is a pivotal brain region implicated in the formation of associative memory.[13–15] It is particularly critical and sensitive to associative memory involving two distinct materials (eg, faces and words) and two different attributes (visual and auditory stimuli).[14,16] Preliminary studies have revealed deficits in visuospatial associative memory in schizophrenia.[17,18] Wannan et al followed up first episode psychosis and observed that visuospatial associative memory deteriorated significantly as the disease progresses.[18] Moreover, previous neuroimaging investigations have suggested that deficits in associative memory in schizophrenia are associated with abnormalities in hippocampal structure and function.[17,19–22] Therefore, the hippocampus may be a potential therapeutic target for associative memory deficits in schizophrenia.

Researchers have indicated that abnormal functional connectivity within the hippocampus and lateral prefrontal cortical(PFC) network in individuals at Clinical High-Risk for Psychosis, first-episode and chronic schizophrenia.[23] A meta-analysis has revealed increased glutamate levels in the hippocampus and prefrontal lobes, along with decreased Gamma-Aminobutyric Acid (GABA) levels in the cingulate gyrus.[24] It has been proposed that cognitive deficits in schizophrenia may result from the derepression of glutamatergic pyramidal neurons, leading to glutamatergic hyperfunction in the hippocampus.[25,26] The hippocampus exports excess glutamate to the downstream prefrontal cortex, resulting in dysfunctional inhibition of GABAergic parvalbumin proteins within the prefrontal cortex and is associated with a decrease in r-wave oscillatory activity. Functional activity in the prefrontal lobes and hippocampus is significantly increased in patients at high risk for psychosis during an associative memory task.[20] Resting-state functional magnetic resonance imaging (rs-fMRI) studies have found that associative memory deficits in schizophrenia are associated with reduced functional connectivity in the hippocampus and medial temporal lobe(MTL).[27] Enhanced hippocampal connectivity to areas known to be active during memory retrieval, including medial prefrontal, inferior parietal and parahippocampal cortices, has been demonstrated during memory retrieval in two large-scale normal human fMRI studies.[28] Defective hippocampal resting-state precuneus functional connectivity and elevated hippocampal glutamate abnormalities have been reported in patients with schizophrenia.[29] It has been suggested that the enhancement of hippocampal resting-state functional connectivity (rsFC) and episodic memory induced by repetitive transcranial magnetic stimulation (rTMS) is mediated through the propagation of neural activity and subsequent synaptic modifications via either the left parietal cortical-parahippocampal or parietal cortical-retrosplenial pathways .[30] Consequently, targeting the dorsolateral prefrontal cortex (DLPFC)-hippocampus or lateral parietal cortex (LPC)-hippocampus pathways may represent a viable intervention strategy for addressing associative memory deficits in individuals with schizophrenia.

Studies have shown that rTMS stimulation of specific brain regions in the cortex can modulate hippocampal function.[31,32] Since traditional rTMS coils cannot directly stimulate deep regions such as hippocampus area in the brain, current studies regulate the hippocampus function by stimulating the cortico-hippocampal functional network, which is composed of the DLPFC, the LPC, and hippocampal structures.[33–36] Among which the hippocampus is connected to the neocortex via the parahippocampal gyrus.[35] Bilek et al applied high-frequency rTMS to stimulate the right DLPFC in healthy volunteers and found that rTMS improved prefrontal-hippocampal functional connectivity and interaction.[36] Wang et al applied high-frequency rTMS to stimulate the left LPC of healthy volunteers for 5 days and discovered that rTMS could improve parietal-hippocampal functional connectivity and associative memory. Additionally, they found a correlation between functional connectivity changes and associative memory improvement that lasted for at least 15 days.[33,34] However, no studies have been found on improving hippocampal function in schizophrenia by intervening in the hippocampus and its abnormal functional network.

Theta burst stimulation (TBS) is a new modality of rTMS, consists of a burst of three stimuli at 50 hz and is repeated at 200 ms intervals. Depending on the form of pulse delivery, TBS is divided into intermittent TBS (iTBS) and continuous TBS (cTBS). It can alter cortical excitability, induce long-term potential(LTP)or long-term depression-(LTD)and modify synaptic plasticity.[37] Compared with traditional rTMS, TBS has a lower stimulus intensity and can change cortical excitability in a shorter period of time (3–4 min), significantly reducing treatment time and increasing

patient compliance.[38,39] In addition, the frequency of the pulses delivered by TBS coincided with the frequency of the hippocampal theta rhythm, which is associated with memory storage.[40] Current theories suggest that iTBS increases cortical excitability and induces an LTP effect,[38] which is associated with memory formation.[40]

In this study, we performed a randomized, double-blind, sham-controlled trial of the efficacy of rTMS on associative memory in schizophrenia patients. We hypothesized that applying the iTBS mode of rTMS to the left lateral parietal cortex (LPC) or the right dorsolateral prefrontal cortex (DLPFC) of schizophrenia would modulate hippocampal function and its functional network, and thus improve symptoms such as situational memory deficits in schizophrenia.

# Materials and Methods

## Participants and Study Design

This prospective, randomized, double-blind (participants and outcome assessors), parallel, sham-controlled study, included two random procedures, which were the stimulation site (right DLPFC or left LPC) and active or sham. The participants were recruited from the inpatients of Shanghai Mental Health Center (SMHC) between April 1, 2019 to December 31, 2021. All were Han nationality, right-handed, and had normal vision or corrected-to-normal vision. All were interviewed with the Mini International Neuropsychiatric Interview (M.I.N.I 7.0).[41] At recruitment, all patients were aged 18 to 50 years old and met the criteria for schizophrenia (Using the Diagnostic and Statistical Manual of Mental Disorders-fifth edition) .All participants were required to maintain the antipsychotic regimen for at least 30 days after enrollment, which have been agreed by the treating physician, participants and their families. Meanwhile, all the subjects were clinically stable (defined as no change in second generation antipsychotics for at least 6 weeks before randomization). Exclusion criteria included patients with mental retardation, dependence on psychoactive substances (such as nicotine and alcohol), a comorbid unstable physical illness, a current pregnancy or lactation period, received modified electroconvulsive therapy (MECT) in the last 6 months, or any contraindication to MRI and rTMS treatment.

## Ethical Considerations

The study was approved by the Ethics Committee of the Shanghai Mental Health Center (2018–38R) and registered with clinicaltrials.gov (NCT03608462). All subjects obtained informed consent, voluntarily participated in the study, and signed a written informed consent form. This study has been conducted in accordance with the Declaration of Helsinki.

## Clinical Assessments

Psychopathology (positive, negative and general) was assessed by using the Positive and Negative Syndrome Scale (PANSS),[42] Clinician-Rated Dimensions of Psychosis Symptom Severity (CRDPS),[43,44] Clinical Global Impression-Severity (CGI-S).[45] Negative symptoms were assessed in detail using the Scale for the Assessment of Negative Symptoms (SANS).[46] Accompanying depressive symptoms were assessed using the Calgary Depression Scale for Schizophrenia (CDSS).[47]

## Associative Memory Performance

The associative memory paradigm of this study was adapted from Borders et al, included visual-visual (Vis-Vis), auditory-auditory (Aud-Aud), and visual-auditory (Vis-Aud) pairing task.[48] The experimental format was computer screen/headset presentation and numeric keypad manipulation. To discourage the "verbalization", we used abstract visual and meaningless auditory stimuli. Visual stimuli were derived from a pool of 250 fractal graphs (Figure 1) from the Internet and resized to 320*240 pixels. Auditory stimuli were drawn from a pool of 243 non-verbal, non-representative, and meaningless sound clips found online and produced by Audacity sound editing software (https://www.audacityteam.org/). All sound fragments were edited to a duration of 2s and consistent with sound intensity.

Each of the three associative memory tasks consists of a learning phase and a testing phase. During the learning phase, a series of stimulus pairs were presented at a frequency of 4s. Participants were required to link the items together and try to remember the pairings. After each group of stimuli was presented, the subjects used the four-point judgment scale (1= no link, 4= strong link) to judge the degree of correlation between the two stimuli (Figure 1).During the testing

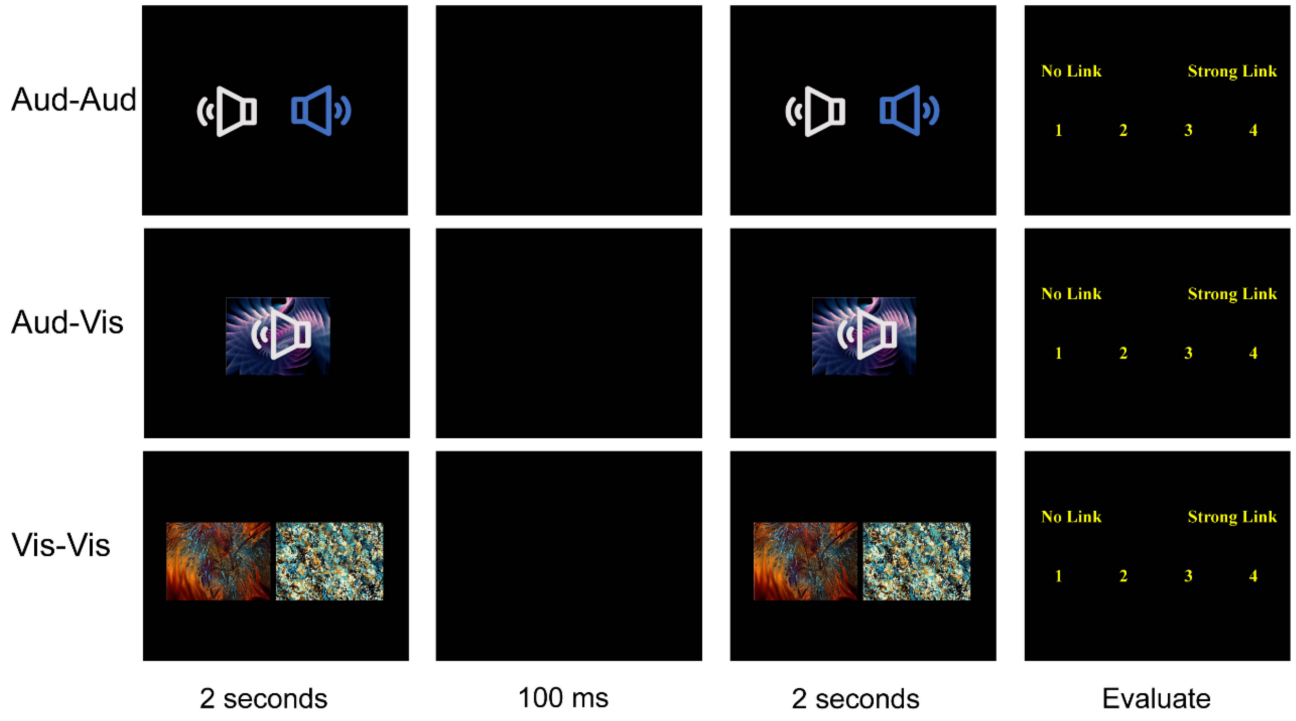


**Figure 1** Schematic of study trails for each condition. The stimulus presentation pattern in the testing phase was the same as that in the learning phase. In the learning phase, the subjects used the four-point judgment scale to judge the degree of correlation between the two stimuli. In the testing phase, the participants used 6-point confidence scale to judge whether the present pairs were "intact" or "rearranged".

phase, the rate of stimulus pairing presentation was same with the learning phase. Rearranged tasks (new matching tasks) were added, intact (learned matching task) and rearranged trials were presented randomly. The participants used 6-point confidence scale (1= sure rearranged 2= maybe rearranged, 3= guess rearranged, 4= guess intact, 5= maybe intact, 6= sure intact) to judge whether the present pairs were "intact" or "rearranged". 5s breaks between the learning phase and the testing phase, but the responses were self-paced and the confidence scale remained visible until a response was entered.

In the Aud-Aud task, two different sound stimuli are presented simultaneously through the left and right channels of the headset for 2s, then repeated for another 2s with an interval of 100ms.Each sound stimulus was presented through the same vocal tract of the headset (left or right) during the learning and testing phases. After completing a session, E-PRIME recorded the subject's response data. In the Vis-Vis condition, two fractal images were presented side by side in the center of the screen for 2s, then repeated for another 2s with an interval of 100ms. Each picture stimulus was presented on the same side of the screen (left or right) during the learning and testing phases. Vis-Vis pairing task and Vis-Aud pairing task were divided into two tests, with 24 learning-testing blocks. Each learning list contained 24 stimulus pairs, and each testing list contained 24 stimulus pairs (a mixture of 12 intact and 12 rearranged). In the Vis-Aud task, one picture stimulus was presented in the middle of the screen, while one sound stimulus was played through a dual channel headset for 2s, then repeated for another 2s with an interval of 100ms.

Participants were given an opportunity to practice (to avoid practice effects, visual and auditory stimuli were extracted from a new pool) before the formal experimental task. The generated results were recorded to determine whether participants fully understood the rules. A pre-experiment was conducted on healthy adults before the experiment was administered to patients, eliminating the sounds that could not be discriminated.

## Other Cognitive Assessments and Social Function

To further characterize cognitive function, the MATRICS Consensus Cognitive Battery (MCCB) was selected.[49]

## Treatment with rTMS

### Neuronavigation

Individual neuronavigation using each participant's T1-weighted MRI and navigation system to accurately locate the stimulus target (left LPC or right DLPFC). The MRI images of the participants was collected on a 3.0T Siemens Verio MR scanner (Siemens AG, Erlangen, Germany) with a 32-channel head coil at the Radiology Department of the Shanghai Mental Health Center. The structural MRI and functional MRI was included: ① Three-dimensional (3D) structural MRI: T1-weighted structural image was obtained by applying the Magnetic Preparation Rapid Gradient Echo (MPRAGE) sequence imaging with the following parameters: repetition time (TR) = 2530ms, echo time (TE) = 3.65ms, flip angle (FA)=7°, matrix=256×256, number of pulse repetition excitations (Nex)=1, field of view (FOV)=256×256mm2, layer thickness (thickness)=1mm, layer spacing (Gap)=0, number of layers (slices)=224, and the layers were parallel to the anterior commissure(AC)- posterior commissure(PC) line; ② rs-fMRI: Gradient-Recalled Echo Planar Imaging (GRE-EPI) sequence imaging was applied, with repetition time (TR) = 2000ms, echo time (TE) = 30ms, flip angle (FA) = 90°, matrix (Matrix) = 64×64, Nex = 1, FOV=220×220mm2, layer thickness (thickness)=4mm, layer spacing (Gap)=1mm, number of layers (slices)=30.The stimulation target was accurately located using the navigation system (LOCALITE GmbH, Schloss Birlinghoven, German) according to the 3D reconstruction of the participant's MRI structural image. The right DLPFC stimulation site was in the medial frontal gyrus (Brodmann area 9.46).[50] The left LPC stimulation site was in the angular gyrus (Brodmann area 39).[33,34,51]

### Stimulation Parameters

A MagVenture MagPro X100 repetitive transcranial magnetic stimulation apparatus with an MFC-B56 coil (Medtronic Co., Denmark) was utilized for the delivery of rTMS. The stimulation site was the right DLPFC or the left LPC. The participants were treated with iTBS mode once a day, 5 days per week for 4 weeks. iTBS stimulation mode parameters :80% motor threshold (MT), one short stimulus is issued every 200 ms, three single pulses with a frequency of 50 hz are buried in one short stimulus, and each l0 short stimulus (lasting 2s) has an interval of 8s, a total of 200 short stimulus, and the total stimulation time is approximately 4 min.

### Sham Condition

The sham stimulation coil was used during the intervention and all stimulation parameters were set the same as in the treatment group. The sham approach produces similar vibrations and auditory sound, but no magnetic lines of force were passed through the skull.

## Randomization and Blinding

A total of two randomization procedures were performed. Firstly, subjects were randomly assigned to the DLPFC and LPC groups in a 1:1 ratio. Secondly, subjects were randomly assigned to the active group and sham group in a 2:1 ratio. Through the two randomization processes, patients were randomized into the right DLPFC group, the left LPC group, and the sham group in a 1:1:1 ratio. The randomization list was computer generated. The rTMS technician was aware of the group allocation but was not involved in any clinical or cognitive assessment. Neither the participant nor the rater was aware of the group allocation.

## Statistical Analysis

The sample size was estimated mainly based on the results of Zheng et al's study.[52] We set one-sided test efficacy α= 0.05, the power (1-β) = 0.8. The following formula was applied to calculate the sample size of each group as 24, and considering the attrition rate of 15%, the sample size of each group was 28.

$$N = \frac{(Z_\alpha + Z_\beta)^2 \sigma^2}{\delta^2} (Q_1^{-1} + Q_2^{-1})$$

Statistical significance was set at $P < 0.05$. All analyses were performed using SPSS statistics 27.0 (IBM, Armonk, NY USA).

## Primary Outcome Measure

According to signal detection theory, receiver operating characteristics(ROCs) were used to assess the associative memory performance of the participants, using the false detection rate (1-specificity) as the horizontal coordinate and the specificity of the specificity as the ordinate coordinate.[53] To quantify the associative memory performance, the discriminability d-prime (d') was calculated. First, the response of 1–3 in the 6-level trust level was classified as the "original" response, and the response of 4–6 was classified as the "rearrangement" response. The hit rate (pSN) and false alarm rate (pN) of each group were calculated respectively. The Z value was obtained through the PZO conversion table, and then the d "value was calculated according to the differentiation formula.[54] Repeated measures ANOVA was conducted to evaluate the d" with the sample of completers.

## Secondary Outcome Measure

Completer analysis was conducted. A two-way ANOVA was used to compare the changes in MCCB performance in each cognitive domain pre and post treatment in three groups. Pre and post scores of SANS and PANSS were analyzed by repeated measures ANOVA with iTBS intervention as the between-group factor and time as the within-subject factor.

# Results

Initially 112 participants with schizophrenia were assessed for eligibility. Ultimately, 96 patients were selected for randomization, and 89 of these individuals received the intervention. Of these 89 participants, 61 patients successfully completed treatment and follow-up. Please refer to Figure 2 for the CONSORT chat, Table 1 for the baseline participant characteristics.

## Sample Characteristics

The results showed significant differences in PANSS negative symptom scores between the three groups (F=4.06, p=0.02). However, there were no significant differences in age, gender, education, duration of illness, daily doses of antipsychotic medication, or other baseline psychopathology (p>0.05). Doses were converted to olanzapine equivalents-(OLZ) for comparison.

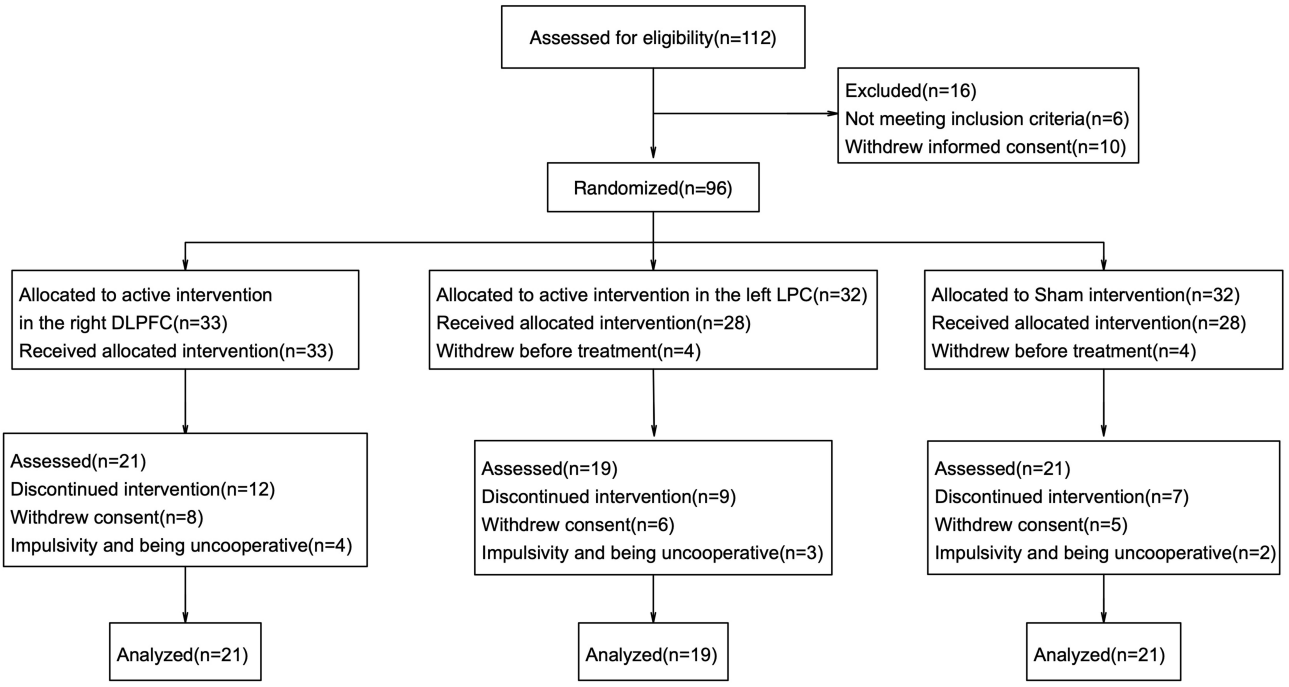


**Figure 2** CONSORT chart for repetitive transcranial magnetic stimulation (rTMS) participant flow, allocation, and randomization.

**Table 1** Demographic and Clinical Characteristics of Active rTMS Group and Sham Group

| Characteristic | Right DLPFC | Left LPC | Sham | Statistical analysis | |
|---|---|---|---|---|---|
| | N=33 | N=28 | N=28 | F/Chi-test | P |
| Demographic data | | | | | |
| Age(years) | 32.06 (10.59) | 34.68 (9.58) | 30.29 (8.86) | 1.55 | 0.22 |
| Gender(M:F) | 10:23 | 12:16 | 16:12 | 4.46 | 0.11 |
| Education(years) | 13.39 (3.27) | 13.82 (3.07) | 14.71 (2.79) | 1.74 | 0.18 |
| Duration of illness(years) | 4.32 (4.67) | 7.64 (7.62) | 4.67 (3.96) | 3.10 | 0.05 |
| OLZ(mg) | 14.53 (6.04) | 15.88 (6.59) | 14.92 (5.04) | 0.63 | 0.70 |
| Baseline psychopathology | | | | | |
| PANSS-total | 67.34 (11.16) | 66.86 (12.87) | 70.50 (13.43) | 0.72 | 0.49 |
| PANSS-positive | 17.00 (5.31) | 17.61 (5.22) | 16.82 (6.48) | 0.15 | 0.86 |
| PANSS-negative | 19.03 (4.99) | 17.68 (6.20) | 22.07 (6.58) | 4.06 | 0.02* |
| PANSS-general | 31.44 (5.85) | 31.21 (6.62) | 32.21 (6.95) | 0.19 | 0.83 |
| SANS | 34.65 (14.86) | 30.15 (18.30) | 39.68 (16.59) | 2.28 | 0.11 |
| CRDPS | 11.61 (3.91) | 11.93 (4.83) | 12.25 (4.54) | 0.15 | 0.86 |
| CGI-SI | 4.58 (0.72) | 4.52 (0.70) | 4.64 (0.56) | 0.24 | 0.79 |
| CDSS | 0.58 (1.15) | 0.56 (1.42) | 1.11 (2.77) | 0.76 | 0.47 |

**Notes**: Values are presented as Mean (SD). PANSS, Positive and Negative Syndrome Scale, SANS, Scale for the Assessment of Negative Symptoms; CRDPS, Clinician-Rated Dimensions of Psychosis Symptom Severity; CGI-SI, Clinical Global Impression-Severity; CDSS, Calgary Depression Scale for Schizophrenia;*For P<0.05.

## The Effects of rTMS on Associative Memory

Out of the 61 participants who completed the treatment, a total of 38 individuals completed the associative memory tasks, with 13 in the right DLPFC group, 13 in the left LPC group, and 12 in the sham group, respectively. The aggregated ROCs of the participants pretreatment and posttreatment are shown in Figure 3. Performance is represented by the distance between the ROC curve and the opportunity diagonal, with poor performance closer to the diagonal. Upon visual examination of the aggregate ROCs, there were no significant differences observed between pre- and post-treatment.

The results indicated that there were no significant differences between intervention group and time interaction on the three types of associative memory. Specifically, we used repeated measures ANOVA to evaluate the d ‘value pre- and post- intervention in the three groups among Aud-Aud associative memory (F=1.27 p=0.294),Aud-Vis associative memory (F= 0.49,p=0.617),Vis-Vis associative memory (F=1.094,p=0.347). No statistical differences were observed in intervention mode and time interaction on the three types of associative memory (Figure 4). After including education, disease duration, and negative symptoms as covariates, iTBS targeting the right DLPFC or left LPC in schizophrenia did not yield significant improvements in Aud-Aud associative memory (F=1.853,p=0.171),Aud-Vis associative memory (F=0.684,p=0.512), or Vis-Vis associative memory (F=0.939,p=0.402).

## The Effects of rTMS on Other Cognitive Function

Prior to treatment, there were no significant differences in MCCB scores among the three rTMS groups (p>0.05). Moreover, the results showed that the interaction of group and time had no significant effect on any of the seven cognitive modules of the patients (Table 2).

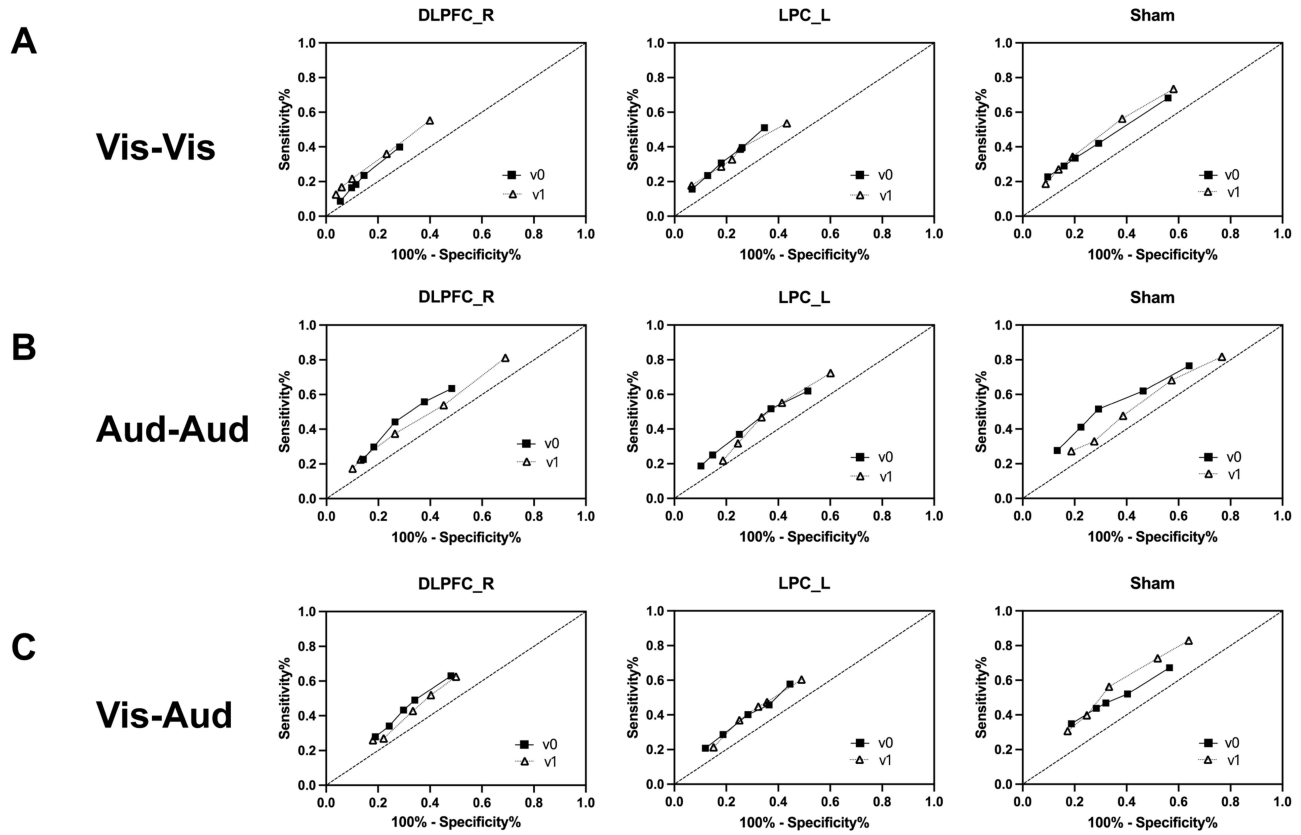


**Figure 3** Aggregated pre and post treatment ROCs. (**A**) Visual-Visual within-domain condition. (**B**)Auditory-Auditory within-domain condition. (**C**) Visual-Auditory across-domain condition. DLPFC_R refers to the active rTMS on the right DLPFC, LPC_L refers to the active rTMS on the left LPC. Sham refers to the sham rTMS on the right DLPFC or left LPC. v0 refers to the associative memory performance at baseline; v1 refers to associative memory performance at the end of treatment.

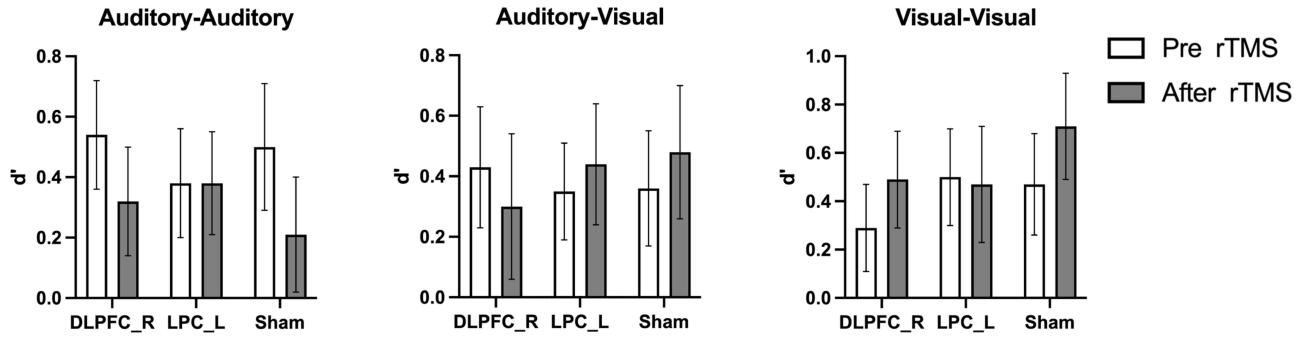


**Figure 4** Aggregated pre and post treatment discriminability for Auditory-Auditory (Aud-Aud), Visual-Auditory (Aud-Vis), Visual-Visual (Vis-Vis) in DLPFC_R, LPC_L and sham group.

## The Effects of rTMS on Psychiatric Symptoms

There was no statistical significance of treatment group and time interaction on the PANSS total score, PANSS positive symptom scores, PANSS negative symptom scores, PANSS general psychopathological symptom scores and SANS total scores ($p>0.05$)(Figure 5).

# Discussion

We are the first study to apply iTBS in hippocampal-cortical memory networks to improve associative memory in patients with schizophrenia. In our study, network-targeted iTBS was applied to the right DLPFC or left LPC in

**Table 2** MCCB Scores of Active rTMS Group and Sham Group Pre and Post Treatment

| Cognitive function (T score) | DLPFC_R(n=15) | | LPC_L(n=10) | | Sham(n=14) | | Group×Time | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre rTMS | After rTMS | Pre rTMS | After rTMS | Pre rTMS | After rTMS | F | P | Partial η2 |
| Speed of processing | 40.53(9.05) | 43.27(11.71) | 42.30(7.57) | 41.30(9.15) | 27.07(10.82) | 33.93(14.41) | 3.04 | 0.06 | 0.16 |
| Attention/Vigilance | 39.60(8.87) | 46.67(11.07) | 42.80(5.05) | 39.30(6.88) | 35.29(15.33) | 37.00(12.44) | 2.98 | 0.07 | 0.15 |
| Working memory | 42.00(12.01) | 47.87(12.85) | 46.50(7.31) | 48.80(6.84) | 43.14(13.97) | 42.00(11.05) | 0.05 | 0.44 | 0.49 |
| Verbal learning | 41.20(12.40) | 40.47(14.02) | 45.90(12.40) | 38.60(9.20) | 38.36(17.47) | 38.79(7.23) | 0.21 | 0.81 | 0.13 |
| Visual learning | 43.93(10.01) | 49.53(7.47) | 48.10(7.55) | 51.40(7.71) | 39.29(15.06) | 46.50(11.75) | 1.37 | 0.27 | 0.08 |
| Reasoning and problem solving | 50.00(9.51) | 49.60(11.85) | 48.40(10.88) | 50.80(11.16) | 42.29(15.27) | 41.71(16.13) | 0.62 | 0.55 | 0.04 |
| Social cognition | 50.40(10.89) | 48.20(13.10) | 43.50(12.82) | 45.60(8.76) | 40.07(9.51) | 40.14(13.38) | 0.36 | 0.70 | 0.02 |
| Neurocognition | 39.40(9.86) | 43.80(9.93) | 43.60(6.47) | 42.40(7.52) | 31.36(17.13) | 35.36(14.80) | 2.78 | 0.08 | 0.14 |
| Overall cognition | 40.33(10.78) | 44.00(10.86) | 42.70(7.75) | 42.20(7.76) | 30.36(17.35) | 34.07(15.77) | 1.97 | 0.16 | 0.11 |

**Notes**: Values are presented as Mean (SD). MCCB, MATRICS Consensus Cognitive Battery; rTMS, repetitive transcranial magnetic stimulation.

schizophrenia to modulate hippocampal-cortical networks and to investigate the effects of rTMS on cognitive function and other symptoms. The primary findings of the study are as follows: 1) iTBS targeting either the right dorsolateral prefrontal cortex DLPFC or the left lateral parietal cortex LPC in individuals with schizophrenia does not enhance associative memory within or across domains. 2) iTBS stimulation does not lead to improvements in cognitive functions

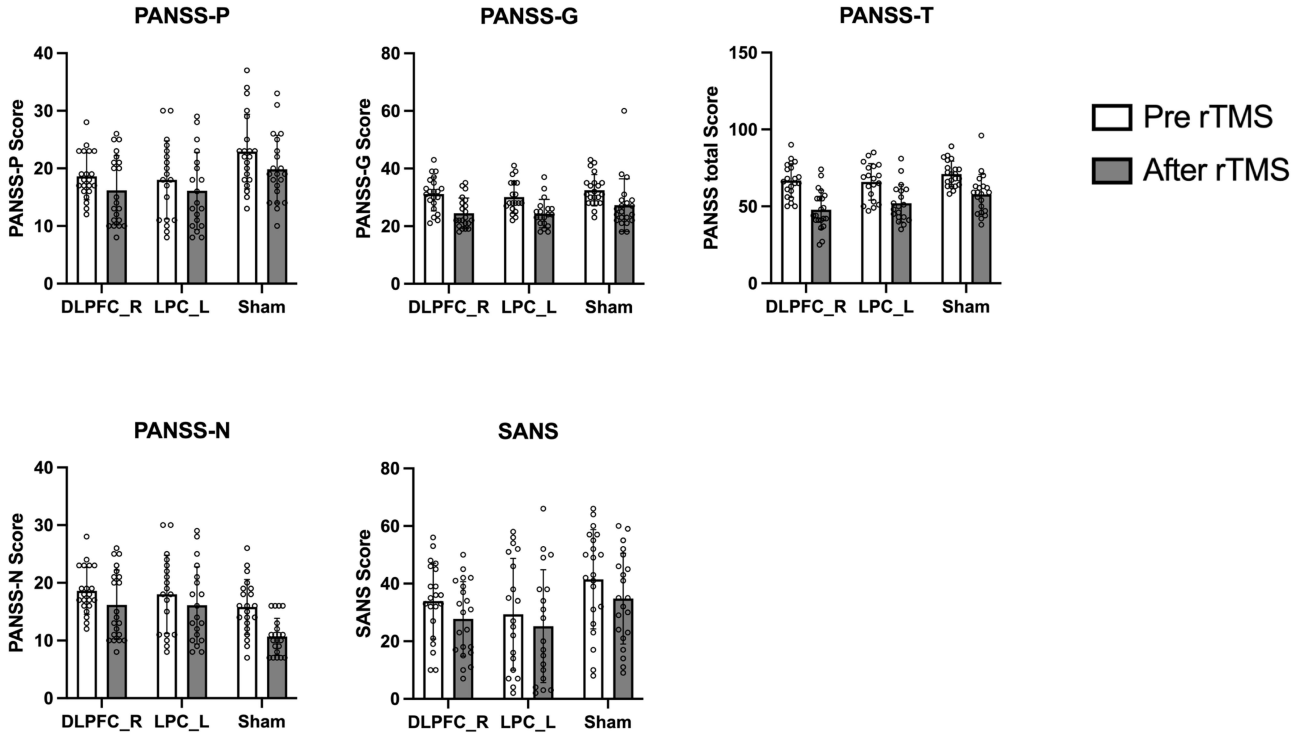


**Figure 5** Aggregated pre and post treatment SANS and PANSS scores within the three groups. Each point represents one subject. SANS: Scale for the Assessment of Negative Symptoms; PANSS: Positive and Negative Syndrome Scale; PANSS-T: PANSS total scores; PANSS-P: PANSS positive symptom scores; PANSS-N: PANSS negative symptom scores; PANSS-G: PANSS general psychopathological symptom scores.

beyond associative memory in these patients. 3) Although rTMS demonstrates a time-dependent effect on psychotic symptoms in schizophrenia patients, neither the main intervention effect nor the interaction effect reaches statistical significance.

Wang et al reported that a 5-day rTMS session targeting the cortical-hippocampal brain network can significantly improve associative memory in healthy subjects.[34] This result was later verified in several studies of healthy individuals. Tambini et al's research showed that cTBS over the right posterior inferior parietal cortex enhances object-location associative memory.[55] Wang's study indicated that 10Hz rTMS on the locations with the strongest cortico-hippocampal connectivity within the lateral parietal cortical or medial prefrontal cortical areas was effective in enhancing face-word recall-based associative memory in the short term.[56] Nilakanta et al used high frequency (20 hz) rTMS to the left lateral parietal lobe of healthy volunteers based on the parietal-hippocampal memory network for 5 days and found that rTMS improved the extraction of episodic memory and reduced the amplitude of event-related potentials (ERPs).[57] However, there are several studies that give conflicting results. Hua et al suggested twice-daily high-frequency rTMS targeting the left inferior parietal lobule was not superior to a previously reported once-daily rTMS group receiving 8,000 pulses, and that the AM scores improvement could not survive the post hoc analysis after multiple comparison correction.[58] Similarly, the study by Gao et al also demonstrated that 5 days of rTMS on individualized IPL targets could not improve AM more than placebo rTMS.[59] Despite administering four days of 20 hz rTMS to a subject-specific region of the left lateral parietal cortex to 39 participants, Hendrikse et al's research failed to yield any evidence of long-lasting enhancement of associative memory or increased parieto-hippocampal connectivity. Instead, functional connectivity within the target network was decreased.[60] A recent systematic review of the effects of rTMS on FC also concluded that rTMS-induced effects are often found outside the targeted network and, overall, do not follow accepted frequency-dependent conventions (ie low frequency (<1 hz) stimulation decreases FC, high frequency (>5 hz) increases FC).[61] Hill et al investigated the effects of cTBS of the DLPFC on associative memory in both healthy young and older adults. Their findings indicated that cTBS did not lead to a reduction in associative memory performance. Given that cTBS primarily inhibits cortical excitability, it may temporarily disrupt the right DLPFC, thereby reducing associative recognition accuracy. However, it is plausible that the monitoring operations supported by the DLPFC are relatively resistant to such manipulations, as they may not significantly restrict access to domain-general processing resources.[62] The research have indicated that accelerate iTBS of the left DLPFC showed an effective and well-tolerated complementary treatment to improve symptoms and cognitive in Alzheimer's disease(AD) patients.[63] Although both schizophrenia and AD have deficits in associative memory, there may be differential deficits in their encoding and retrieval processes that need to be further investigated.

Our study indicated that rTMS targeting on the left LPC or right DLPFC cannot enhance associative memory in schizophrenia. The reasons may be as follows. Firstly, the majority of participants recruited for our study were individuals with chronic schizophrenia, with a mean illness duration of 5.42 ± 5.67 years. Numerous studies have demonstrated that structural and functional brain changes in schizophrenia manifest early in the course of the disease .[64–66] For instance, Schnack et al investigated the rate of structural brain changes in schizophrenia and observed that brain volume atrophy predominantly occurs within the first five years of the illness, after which the rate of atrophy stabilizes to normal levels.[67] This finding implies that chronic schizophrenia may exhibit a diminished responsiveness to treatment compared to early-stage schizophrenia. Secondly, our study utilized nonsensical auditory and visual stimuli to minimize the potential for verbal encoding. In contrast, prior research predominantly employed face-word recall tasks or object-location associations. If participants could label the objects, they might have engaged in within-domain verbal associative memory rather than cross-domain associative memory, potentially influencing the outcomes. Thirdly, unlike previous studies, we implemented the intermittent theta burst stimulation (iTBS) mode in our repetitive transcranial magnetic stimulation (rTMS) protocol. Contemporary theoretical frameworks propose that iTBS enhances cortical excitability, functioning as an "activator".[38] Previous research has demonstrated a top-down inhibitory modulation of the hippocampus by the right dorsolateral prefrontal cortex (DLPFC), which is associated with the process of extracting associative memories .[68,69] We hypothesized that iTBS could activate this inhibitory modulation of the hippocampus by the right DLPFC, thereby suppressing the retrieval of irrelevant memories and enhancing associative memory performance. Concurrently, we posited that iTBS would enhance associative memory by amplifying the modulatory effect

of the LPC on the hippocampus. Contrary to our expectations, our trial did not demonstrate any improvement in associative memory. A meta-analysis demonstrated that iTBS ameliorates negative symptoms and general psychopathological symptoms in individuals with schizophrenia, although it does not significantly impact positive symptoms or cognitive function. Notably, a more pronounced therapeutic effect was observed in patients who received theta-burst stimulation targeting the left DLPFC.[70] Furthermore, another study identified the left DLPFC, ventromedial prefrontal cortex (VMPFC), and the posterior midline cortex (PMC) as primary drivers of network activity during memory retrieval tasks.[71] Additionally, Ma et al (2022) identified functional connectivity between nine subregions of the hippocampus and the prefrontal cortex in healthy subjects, with a notable left hemispheric predominance.[72] This lateralization was also observed in individuals with schizophrenia, indicating abnormalities in the left hippocampus-left dorsolateral prefrontal cortex (DLPFC) pathway.[73] Future research should investigate the modulatory effects of intermittent theta-burst stimulation (iTBS) on the hippocampus, using bilateral DLPFC as the target for intervention. Fourthly, although navigation systems have been employed in repetitive transcranial magnetic stimulation (rTMS) treatment, Cash et al utilized a "seedmap methodology" to compute personalized TMS targets within the lateral parietal cortex (LPC). Their findings indicated that memory performance following multi-session TMS significantly improved only when individuals fortuitously received stimulation in close proximity to the optimized, connectivity-guided personal targets .[74] This suggests that aligning brain stimulation targets according to individual-specific differences in brain connectivity may be crucial. In addition, we do not restrict the use of central anticholinergic drugs (benzodiazepines), as drugs with strong anticholinergic activity may exacerbate the impairment of cognitive function.[75]

In addition to assessing the effects of rTMS on associative memory, we also explored its impact on various other cognitive functions. Our findings indicated no significant improvement in cognitive function following the rTMS intervention. Previous research has yielded heterogeneous results regarding the efficacy of rTMS in treating cognitive deficits associated with schizophrenia.[76] A meta-analysis conducted by Begemann et al reported modest improvements in working memory with rTMS (effect size = 0.17, $p = 0.015$); however, the effects on other cognitive domains were not statistically significant.[77] A systematic review and meta-analysis by Hyde et al included 208 RCTs and showed that rTMS was not superior to pseudo-stimulation for multiple cognitive domains in schizophrenia.[78] Further exploration and research are needed in the treatment of cognitive deficits in schizophrenia.

During iTBS treatment, only three participants reported adverse reactions to headache, and the degree was mild and within the tolerance range. This is slightly consistent with previous studies that iTBS is well tolerated and safe in patients with schizophrenia.[70]

This study has several limitations. Firstly, the sample size is small, potentially resulting in low statistical power. An increased sample size could provide a more robust explanation of the effects of intermittent Theta Burst Stimulation (iTBS) on associative memory and neurocognitive function in individuals with schizophrenia. Secondly, there were baseline differences in negative symptoms among the three groups. Previous research has demonstrated that negative symptoms in schizophrenia can impair cognitive functions, including memory.[79–81] Although our completer analysis did not reveal baseline differences in associative memory among the groups, this factor may still have influenced the results. Thirdly, a number of patients were unable to complete the prescribed 20-session treatment regimen, and several participants discontinued the assessment midway through the administration of the associative memory test, citing the paradigm's excessive difficulty. This led to a relatively high attrition rate. Future studies should consider employing modified associative memory tests and optimized treatment cycles for repetitive transcranial magnetic stimulation (rTMS) to improve its applicability for patients with schizophrenia. Additionally, our study exclusively analyzed behavioral data; incorporating fMRI data analysis could provide a more comprehensive understanding of the modulatory effects of repetitive transcranial magnetic stimulation (rTMS) on the cortico-hippocampal network.

In conclusion, our prospective experiment did not provide evidence that hippocampal-targeted intermittent theta-burst stimulation (iTBS) applied to the left lateral prefrontal cortex (LPC) or the right dorsolateral prefrontal cortex (DLPFC) enhances autobiographical memory (AM) in individuals with chronic schizophrenia. Although this attempt was unsuccessful, it may indicate insufficient intervention intensity or insufficient sample size, offering valuable insights for future research. Recruiting a larger sample size and integrating hippocampal-targeted iTBS with functional magnetic resonance

imaging (fMRI) could potentially elucidate the regulatory role of repetitive transcranial magnetic stimulation (rTMS) in hippocampal regeneration more comprehensively.

## Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article. The data are not publicly available due to ethical restrictions.

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## Disclosure

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work. The authors have no conflicts of interest regarding subject of this paper.

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