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# Effects of transcranial direct current stimulation combined with retrieval practice on semantic memory in patients with schizophrenia

Wen Pan<sup>1,2</sup>, Tiantian Li<sup>1,2</sup>, Xiaofeng Ma<sup>1,2,3\*</sup> and Xiaoning Huo<sup>4</sup>

## Abstract

**Background** The semantic processing deficit stands as a central feature of cognitive abnormalities in schizophrenia. Both transcranial direct current stimulation (tDCS) and retrieval practice have been demonstrated as external techniques capable of ameliorating the semantic processing deficit in individuals with schizophrenia. The inquiry examines whether the combined effect of tDCS and retrieval practice, following tDCS intervention targeting the left dorsolateral prefrontal cortex (L-DLPFC) in patients with schizophrenia, contributes to the preservation of semantic memory in these individuals.

**Methods** We recruited 52 patients diagnosed with schizophrenia from hospitals. After five consecutive days of tDCS intervention (2 mA × 20 mins, twice per day), we administered a word list memorization task comparing retrieval practice and restudy strategies. Subsequently, we observed their immediate and delayed memory performance through tests.

**Results** The semantic memory performance of the anodal group significantly surpassed that of the sham group. There was a significant interaction between stimulation type and learning strategy; regardless of the stimulation modality employed, retrieval practice outperformed restudy strategy. Notably, the semantic memory performance under retrieval practice conditions in the anodal group was significantly superior. ARC clustering scores fully mediate stimulus type and retrieval practice recall rates.

**Conclusions** Continuous periodic tDCS has the potential to enhance the efficacy of retrieval practice strategy, particularly in aiding patients with schizophrenia to improve the maintenance of semantic memory and refine memory organization.

**Trial registration** The present trial has been registered in the American Registry of Clinical Trials Center (ID: NCT06538259) | <http://clinicaltrials.gov/> (Retrospectively Registered Date: 08/03/2024).

**Keywords** Schizophrenia, Transcranial direct current stimulation (tDCS), Retrieval Practice, Semantic memory, Left dorsolateral prefrontal cortex (L-DLPFC)

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## Introduction

The semantic processing deficit is the core cognitive abnormality in schizophrenia [1]. Studies have found abnormalities in the semantic memory structure of schizophrenia patients [2–5]. Semantic memory represents the long-term storage of information [6, 7], and semantic structure is defined based on its cohesion, namely the degree of semantic association between items [8]. Regarding the deterioration of semantic memory structure in schizophrenia patients, there are two theoretical hypotheses. One theory suggests that the memory structure of schizophrenia patients is distorted. Patients with schizophrenia have a significant deficit in semantic storage, with word frequency exaggeration effects and over-initiation [1]. Another theory proposes that schizophrenia patients suffer from poor memory activation. Poor semantic clustering of both low and high frequency category examples in schizophrenics [9]. These results suggest an intriguing possibility that impaired automatic activation of semantic information is a key deficit in schizophrenia [2, 10, 11]. Schizophrenia patients are unable to actively cluster their information. Non-invasive neurostimulation technique transcranial direct current stimulation (tDCS) and behavioral technique retrieval practice (RP), based on different principles, contribute to improving semantic processing deficits in schizophrenia patients through passive intervention and active learning.

### The role of tDCS in semantic processing deficits in schizophrenia

Transcranial direct current stimulation (tDCS) emerges as a promising avenue to bolster cognitive function by enhancing neuroplasticity, offering a non-invasive and innocuous method of brain stimulation [12, 13]. It modulates the intrinsic neural activity and associated neural networks in the targeted brain area through the application of subtle electrical currents externally [14]. Neurobiologically, schizophrenia is delineated as a disorder characterized by impaired neuroplasticity [15], with perturbations in  $\gamma$ -aminobutyric acid (GABA) and glutamate neurotransmission, and dysfunction in the N-methyl-D-aspartate receptor (NMDAR)/glutamate system, situated amidst primary and secondary glutamatergic neurons, may underlie the pathology of schizophrenia [16, 17]. Impairment of NMDA receptors, in turn, precipitates diminished function of GABAergic interneurons [18]. tDCS augments the inhibitory function of GABA with minimal adverse effects [19, 20], thereby ameliorating cognitive function. Activation in left frontal regions is associated with categorical clustering in a recalled verbal learning task [21]. Intervention with tDCS over the L-DLPFC during word encoding processes enhances semantic organizational strategies [22]. Prior investigations have underscored the pronounced role of tDCS in

improving semantic categories and bolstering semantic memory organization in schizophrenia patients [23].

### The role of retrieval practice in semantic processing deficits in schizophrenia

Retrieval practice (RP) is a behavioral technique aimed at actively prompting individuals to retrieve information from memory, facilitating easier recall of the retrieved information in the future [24]. The retrieval practice effect denotes that, within an equivalent time-frame, retrieving learning materials once or multiple times yields more enduring memory retention and superior knowledge transfer in the future compared to mere restudying of the materials [25–28].

When it comes to cognitive correction for individuals with schizophrenia, cognitive training methods are predominantly employed [22]. Although continuous cognitive training can enhance cognitive performance, as performance improves, these exercises progressively become more challenging. On the other hand, strategic techniques like retrieval practice offer a more direct and effective means to enhance cognitive performance [29, 30]. Retrieval practice serves as a cognitive remediation strategy for individuals with schizophrenia [31]. Implementing retrieval practice on schizophrenia patients and observing their semantic association performance revealed that the semantic relational memory deficits in schizophrenia primarily stem from the difficulty in initiating semantic memory strategies [32, 33]. However, retrieval practice can help patients perform active retrieval, thereby inducing a fine-grained encoding of semantics that promotes the refinement of semantic representations and improves memory performance [34, 35].

### Present study

Research on semantic memory in schizophrenia patients has revealed weaker activation in the prefrontal cortex, potentially linked to cognitive impairments [36, 37]. Prior studies have suggested that continuous periodic tDCS intervention in the left dorsolateral prefrontal cortex (L-DLPFC) can enhance semantic recognition abilities [38]. Semantic memory organization in schizophrenia patients approaches that of healthy individuals after undergoing continuous tDCS stimulation of the left DLPFC for five days, ten times [5]. Thus, stimulating the excitability of the L-DLPFC through tDCS can effectively ameliorate semantic memory impairments in schizophrenia patients and is the preferred area for interventions in semantic memory treatment.

As an effective learning strategy, retrieval practice can assist patients in enhancing semantic elaboration and boosting memory performance [31]. Research utilizing near-infrared brain imaging technology to observe brain regions during retrieval practice has revealed that during

challenging word retrieval tasks, activation levels in the inferior frontal gyrus, Frontal polar region, and dorsolateral prefrontal cortex area are significantly higher compared to conditions without retrieval, aligning closely with the regions activated by tDCS [39]. This suggests that there is consistency in brain activation between tDCS and retrieval practice, and combining the two may result in mutually reinforcing effects.

A study involving 119 healthy subjects investigated the combination of tDCS intervention with retrieval practice and found that the strong retrieval practice effect left no room for tDCS to improve memory performance [40]. The combination of single-session online tDCS with retrieval practice in healthy individuals and found that the memory performance of anodal stimulation was inferior to cathodal stimulation and sham stimulation [41]. We have already explored the role of continuous periodic tDCS combined with interim testing on spatial route learning in patients with schizophrenia in a previous study [42], and found that both the learning strategy and tDCS independently facilitated the ability of patients with schizophrenia to learn new information in spatial route learning, suggesting that the tDCS of L-DLPFC has a significant improvement effect. In contrast, targeted tDCS treatment may be more effective for memory-impaired populations such as schizophrenia [43]. Therefore, further investigation is needed to determine the effectiveness of combining tDCS and retrieval practice for semantic memory intervention in schizophrenia patients. From a theoretical perspective, this combination may have a dual activation effect because (1) tDCS stimulation can enhance activation levels of the L-DLPFC, improving its cognitive function impairment;

(2) retrieval practice can not only help patients initiate semantic memory strategies and promote semantic elaboration but also actively activate the brain regions stimulated by tDCS, thereby producing a synergistic effect [34, 35].

Therefore, this study aims to examine whether the combination of tDCS and retrieval practice enhances the maintenance of semantic memory and improves semantic organization by comparing retrieval practice strategies between patients receiving anodal L-DLPFC stimulation and those receiving sham stimulation.

## Methods

### Participants

As reported in a previously published study [42], 55 inpatients with schizophrenia were recruited from a mental health center. Among them, three patients were discharged due to unwillingness to cooperate with the stimuli (1 in the anodal group, 1 in the sham group) or illness (1 in the anodal group due to influenza). Ultimately, 52 patients completed the treatment and participated in the experiment ( $M_{age} = 36.38$ ,  $SD = 10.12$ ; 24 females). All participants provided written informed consent.

Patients with schizophrenia were diagnosed and assessed by two chief psychiatrists. Patients were assessed prior to enrollment using the Montreal Cognitive Assessment (MoCA) scale [44] to evaluate general cognitive function and the Positive and Negative Syndrome Scale (PANSS) [45] for clinical symptoms. To ensure homogeneity in participant allocation, patients were alternately assigned to the anodal group and the sham group based on their PANSS and MoCA assessment results. During the experiment, both groups received tDCS stimulation for the same duration. For the sham group, the current was automatically reduced to 0 mA by the tDCS device during the ramp-up and ramp-down phases, each lasting 10 s. Throughout the entire experiment, only one investigator responsible for administering the tDCS stimulation was aware of the group assignments, while all other investigators involved in data collection were blinded to the participants' group assignments. The characteristics of the participants are presented in Table 1, showing no significant differences in participant characteristics between the two stimulation types groups.

Patients with schizophrenia were included based on the following criteria: (1) meeting the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); (2) aged 18 years or older, regardless of gender, with an educational level of elementary school or above; (3) all patients received stable-level antipsychotic medication treatment, were in a stable phase of disease treatment, able to understand the testing requirements, and cooperated to complete all research tasks (Stability is defined

**Table 1** Characteristics of participants

Variables	Anodal M ± SD (range)	Sham	p
Age(year)	36.22 ± 9.47 (21–58)	36.56 ± 10.97 (19–60)	0.906
Age at onset(year)	26.18 ± 8.83 (14–56)	26.60 ± 8.48 (12–43)	0.864
Duration of illness(year)	10.03 ± 6.95 (1–27)	9.96 ± 7.65 (0–28)	0.970
Education(year)	11.07 ± 3.66 (6–18)	10.48 ± 4.27 (3–24)	0.592
PANSS Positive syndrome	13.66 ± 3.22 (10–22)	15.16 ± 4.00 (10–24)	0.144
PANSS Negative syndrome	21.44 ± 4.06 (14–32)	21.16 ± 2.88 (15–27)	0.774
PANSS General psychopathology	40.66 ± 5.37 (32–51)	37.72 ± 8.70 (20–54)	0.145
PANSS Total	76.88 ± 9.47 (61–93)	74.00 ± 12.18 (53–100)	0.342
MoCA	19.85 ± 2.24 (14–24)	18.76 ± 2.78 (12–24)	0.125

Note. PANSS=Positive and Negative Syndrome Scale. MoCA=Montreal Cognitive Assessment

as the use of antipsychotic medication at a stable therapeutic dose, with no evident signs of acute exacerbation or symptom aggravation); (4) no history of neurological disorders or other serious physical illnesses, and no history of intellectual disability; (5) no color blindness, color weakness, or other color vision impairments, with normal vision or corrected vision.

Exclusion criteria were as follows: (1) clear cognitive impairment caused by somatic or cerebral organic lesions, such as cerebrovascular diseases, traumatic brain injury, etc.; (2) individuals with mental disorders caused by substance dependence or abuse, or the use of psychoactive substances; (3) history of brain injury or other central nervous system-related organic diseases; (4) individuals at significant risk of suicide or harming others; (5) participation in similar experiments in the past 30 days prior to baseline.

### Design

A mixed experimental design of 2 (Stimulation type: anodal stimulation, sham stimulation)  $\times$  2 (Learning strategy: retrieval practice, restudy)  $\times$  2 (Retention interval: Immediate recall, Delayed recall) was employed. Stimulation type was a between-subjects variable, while learning strategy and testing time were within-subject variables. The dependent variables were the correct recall rate and Adjusted Ratio of Clustering (ARC) scores in the testing phase.

### Devices and materials

#### Devices

The direct current stimulation device powered by batteries used in this study was the Starstim system from NE (Neuroelectronics) company in Spain. All groups utilized the same electrode montage, and the electrode placement followed the international 10–20 system for electroencephalography. The tDCS intervention employed 8 cm<sup>2</sup> circular sponge electrodes. The anode was placed over F3 (i.e., L-DLPFC) and the cathode over FP2 (i.e., right supraorbital area).

#### Materials

Thirty-four words from eight common semantic categories were selected as the learning materials. Among them, five words were chosen from each of the six categories (fruits, clothing, musical instruments, sports, stationery, media) as experimental items, while two words were selected from each of the remaining two categories (daily necessities, body organs) as filler items. These filler items were presented at the beginning and end of the learning list to control for primacy and recency effects, respectively.

The selection of experimental categories followed the following rules: (1) To control for the mutual influence

between categories, relatively unrelated categories were chosen (the main control was the degree of association between categories and their knowledge domains, such as choosing between fruits and vegetables); (2) Two-character words with clear semantics were selected as sample words. The selection of sample words followed these rules: (1) Each sample word was a two-character word with clear semantics; (2) Each sample word had a different pronunciation [46].

Prior to the formal experiment, 20 schizophrenia patients were randomly selected as participants to assess the semantic familiarity and relevance of 30 pairs of category sample word pairs. Evaluation was conducted on a Likert five-point scale (1 indicating complete unfamiliarity or no relation, and 5 indicating complete familiarity or very close relation). The results indicated that there were no significant differences between the familiarity ( $M=4.42$ ,  $SD=0.76$ ) and relevance ( $M=4.75$ ,  $SD=0.47$ ) of the retrieval practice list (fruits, clothing, instruments) and the familiarity ( $M=4.61$ ,  $SD=0.59$ ) and relevance ( $M=4.65$ ,  $SD=0.45$ ) of the restudy list (sports, stationery, media),  $t(19) = -1.765$ ,  $p=0.094$ , 95% CI [-0.41, 0.03],  $t(19)=1.344$ ,  $p=0.195$ , 95% CI [-0.05, 0.25].

### Procedure

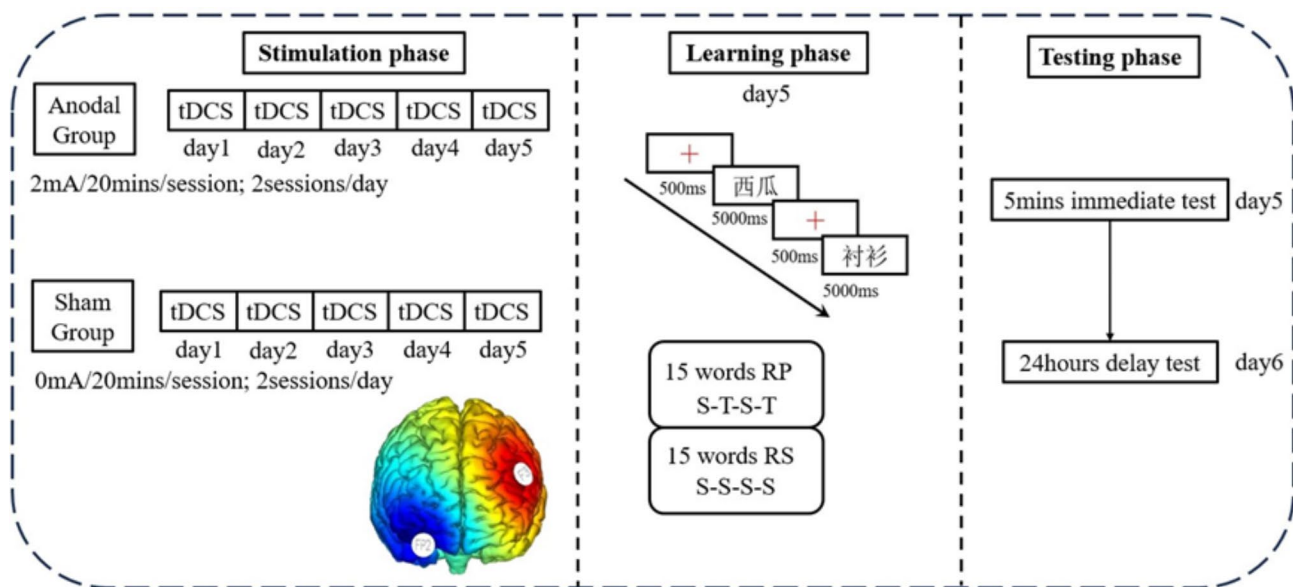
Treatment was administered by two examiners, and after a total of 10 sessions over 5 consecutive days, a final group of 52 patients participated in the learning and testing phase. Among them, 27 received anodal stimulation, while 25 received sham stimulation. Each participant of each stimulation type was involved in both learning conditions, meaning that all participants completed both retrieval and restudy learning and testing (experimental procedure in Fig. 1).

#### Stimulation phase

In the anodal group, the anode was placed over the left DLPFC (F3), and the cathode was placed over the contralateral supraorbital area (FP2). A direct current of 2 mA was applied for 20 mins during each stimulation session. Stimulation was conducted twice a day, at 9 a.m. and 2 p.m., for 5 consecutive days, totaling 10 sessions. In the sham group, the stimulation parameters, including the stimulation site and duration, were identical to those of the anodal group. However, during the 10-second ramp-up and ramp-down periods preceding and following the stimulation, patients were unaware that the voltage had been turned off.

#### Learning phase

The experimental procedure followed the classic retrieval practice paradigm, which included a learning phase and a final test phase.



**Fig. 1** Experiment procedure

During the experiment, participants were informed that they would learn two lists of words. Subsequently, they might either learn the words again or complete a list recall test, and will be given a final test shortly thereafter. The learning of the retrieval practice list and the restudy list was conducted in a randomly balanced manner. Each word was presented for 5 s, with a 500-millisecond interval between words. To avoid providing secondary retrieval cues between examples, all words were shuffled pseudo-randomly within categories. Each list contained 17 words, consisting of 5 examples from each of the 3 experimental categories (15 experimental examples, 2 filler examples). The first and last words presented in each list were filler words, thus controlling for the primacy and recency effects on memory.

For the retrieval practice list, participants underwent two learning sessions and two retrieval sessions (S-T-S-T). During retrieval, participants were instructed to write down all the words they had just remembered within 5 min. For the restudy list, participants underwent four study sessions (S-S-S-S). Between each learning cycle, participants completed a 3-minute simple arithmetic task (dispersed attention task).

### Testing phase

**Immediate Test:** Participants were instructed to recall as many words as possible from the learned lists within 10 mins after completing all learning tasks.

**Delayed Test:** Participants were informed to recall as many words as possible from the learned lists within 10 mins 24 hours later.

### Date scoring & analysis

The experimental results were processed using SPSS 26.0. The correct recall rate of word lists was calculated for each subject by the experimental assistant. Then, Free recall organization was measured by the Adjusted Ratio of Clustering (ARC) scores [47, 48]. ARC scores range from -1 to 1. An ARC score of 0 indicates a level of clustering comparable to that expected by chance, while a score of 1 represents perfect clustering. Negative ARC scores reflect atypical recall patterns that are challenging to interpret [49]. For that reason, negative scores were excluded from analyses.

A mixed-design analysis of variance (ANOVA) was conducted to compare the correct recall rates and ARC clustering scores between the two learning strategies under two stimulation conditions. All statistical tests were performed at a significance level of 0.05, and post-hoc comparisons were adjusted using Bonferroni correction. Effect sizes were reported using partial eta-squared ( $\eta_p^2$ ; ANOVAs).

A mediation analysis was conducted to explore whether ARC clustering scores mediate the relationship between stimulation type and correct recall of word lists. The mediation effect was tested with reference to the Bootstrap method proposed by Hayes [50], using PROCESS 4.1 of SPSS 26.0, selecting model 4, with a sample size of 5000 at 95% confidence intervals, with stimulus type as the independent variable  $X$  (assigned as anodal = 1, sham = 0), the rate of correct recall of retrieval practice as the dependent variable  $Y$ , and ARC scores as the mediator variable  $M$ .



## Results

### Final recall test

As shown in Fig. 2, results indicated a significant main effect of stimulation type,  $F(1,50)=7.436$ ,  $p<0.01$ ,  $\eta_p^2 = 0.129$ , Bonferroni post-hoc comparisons revealed that correct recall rate was significantly higher for Anodal stimulation ( $M = 0.30$ ,  $SD = 0.02$ ) compared to Sham stimulation ( $M = 0.20$ ,  $SD = 0.02$ ),  $p < 0.01$ ,  $d = 5.00$ , 95% CI [0.02, 0.16], indicating a significant effect of tDCS stimulation. There was also a significant main effect of learning strategy,  $F(1,50) = 38.650$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.436$ . Correct recall rate was significantly higher for Retrieval practice ( $M = 0.32$ ,  $SD = 0.02$ ) compared to Restudy ( $M = 0.17$ ,  $SD = 0.01$ ),  $p < 0.001$ ,  $d = 9.48$ , 95% CI [0.10, 0.19], indicating a significant advantage of retrieval practice over restudy. Additionally, a significant main effect of retention interval was observed,  $F(1,50) = 20.759$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.293$ . Correct recall rate was significantly higher for Immediate recall ( $M = 0.28$ ,  $SD = 0.02$ ) compared to Delayed recall ( $M = 0.22$ ,  $SD = 0.01$ ),  $p < 0.001$ ,  $d = 3.79$ , 95% CI [0.03, 0.08].

Further analyses of the interaction effect of stimulation type and learning strategy were conducted in the immediate and delayed recalls respectively. In the immediate recall (Fig. 2A), a significant interaction effect was found between stimulation type and learning strategy  $F(1,50)=4.455$ ,  $p<0.05$ ,  $\eta_p^2 = 0.082$ . Within the Anodal group, correct recall rate was significantly higher for Retrieval practice ( $M=0.44$ ,  $SD=0.03$ ) compared to Restudy ( $M=0.23$ ,  $SD=0.03$ ),  $p<0.001$ ,  $d=7.00$ , 95% CI [0.13, 0.28]. Within the Sham group, correct recall rate was significantly higher for Retrieval practice ( $M=0.28$ ,  $SD=0.03$ ) compared to Restudy ( $M=0.18$ ,  $SD=0.03$ ),  $p<0.05$ ,  $d=3.33$ , 95% CI [0.02, 0.17].

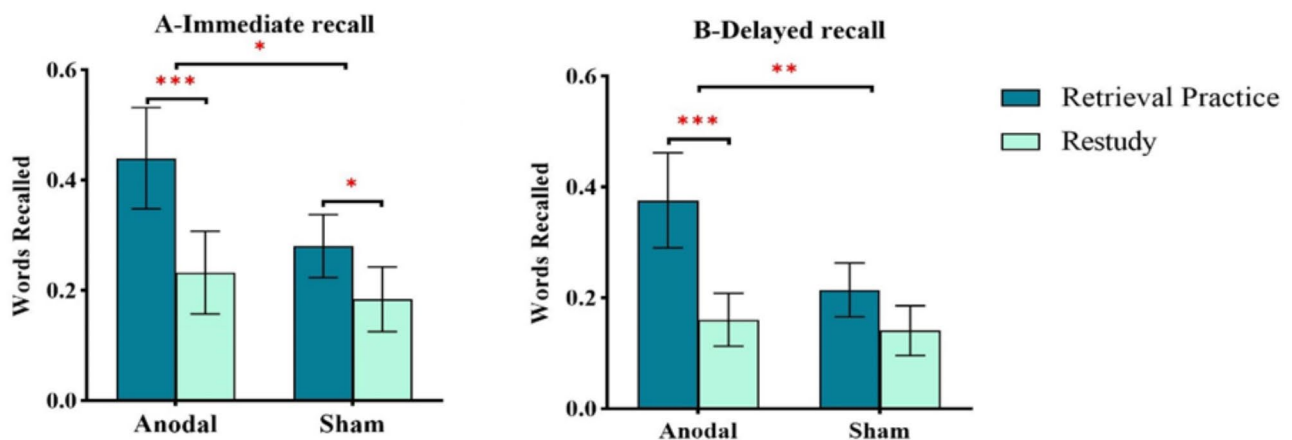
In the delayed recall (Fig. 2B), a significant interaction effect was found between stimulation type and learning

strategy  $F(1,50)=7.911$ ,  $p<0.01$ ,  $\eta_p^2 = 0.137$ . Within the Anodal group, correct recall rate was significantly higher for Retrieval practice ( $M=0.37$ ,  $SD=0.03$ ) compared to Restudy ( $M=0.16$ ,  $SD=0.02$ ),  $p<0.001$ ,  $d=8.23$ , 95% CI [0.14, 0.28]. Within the Sham group, the correct recall rate was not significantly different for Retrieval Practice ( $M=0.21$ ,  $SD=0.03$ ) compared to Restudy ( $M=0.14$ ,  $SD=0.02$ ),  $p=0.055$ ,  $d=2.74$ , 95% CI [-0.00, 0.14].

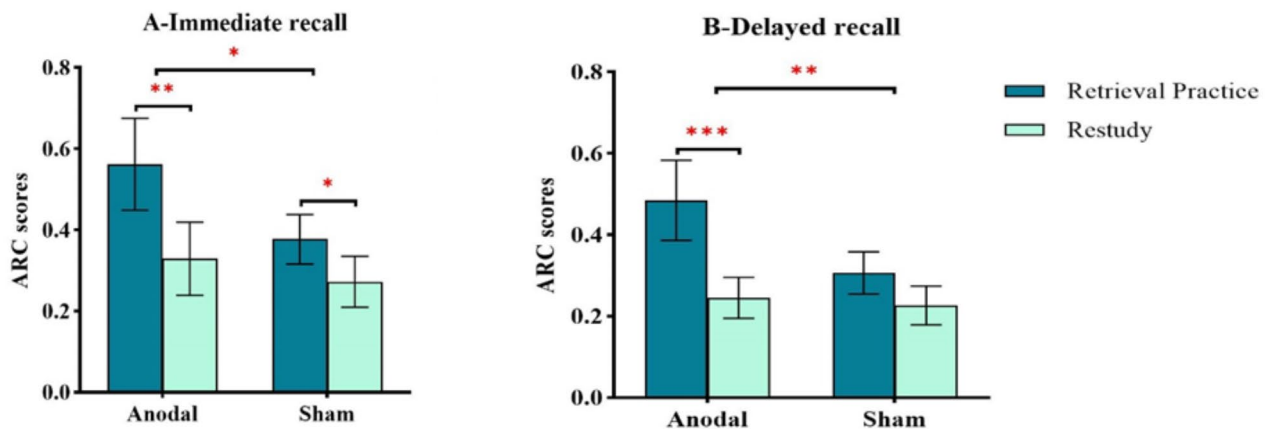
### ARC scores

As shown in Fig. 3, results revealed a significant main effect of stimulation type,  $F(1,50)=6.949$ ,  $p<0.05$ ,  $\eta_p^2 = 0.122$ . Bonferroni post-hoc comparisons indicated that the ARC score was significantly higher for Anodal stimulation ( $M=0.40$ ,  $SD=0.02$ ) compared to Sham stimulation ( $M=0.29$ ,  $SD=0.03$ ),  $p<0.05$ ,  $d=4.31$ , 95% CI [0.02, 0.19], suggesting a significant effect of tDCS stimulation. There was also a significant main effect of learning strategy,  $F(1,50)=38.076$ ,  $p<0.001$ ,  $\eta_p^2 = 0.432$ . The ARC score was significantly higher for Retrieval practice ( $M=0.43$ ,  $SD=0.02$ ) compared to Restudy ( $M=0.26$ ,  $SD=0.02$ ),  $p<0.001$ ,  $d=8.50$ , 95% CI [0.11, 0.21], indicating a significant advantage of retrieval practice over restudy. Additionally, a significant main effect of retention interval was observed,  $F(1,50)=19.528$ ,  $p<0.001$ ,  $\eta_p^2 = 0.281$ . The ARC clustering score was significantly higher for Immediate recall ( $M=0.38$ ,  $SD=0.02$ ) compared to Delayed recall ( $M=0.31$ ,  $SD=0.01$ ),  $p<0.001$ ,  $d=4.42$ , 95% CI [0.03, 0.10].

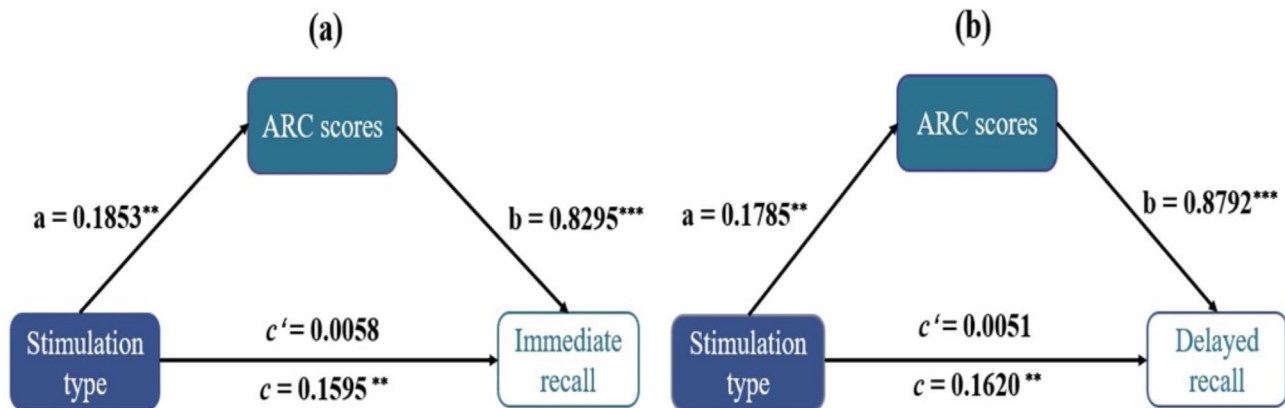
Further analyses of the interaction effect of stimulation type and learning strategy were conducted in the immediate and delayed recalls respectively. In the immediate recall (Fig. 3A), a significant interaction effect was found between stimulation type and learning strategy  $F(1,50)=4.730$ ,  $p<0.05$ ,  $\eta_p^2 = 0.086$ . Bonferroni post-hoc comparisons showed that within the Anodal group,



**Fig. 2** (A) Mean proportion of words immediate recalled (B) Mean proportion of words delayed recalled. Error bars represent standard error of the means. \* $p<0.05$ , \*\* $p<0.01$ , \*\*\* $p<0.001$



**Fig. 3** (A) ARC scores in the immediate recall (B) ARC scores in the delayed recall. Error bars represent standard error of the means. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$



**Fig. 4** Mediation model diagram between Stimulation type and correct recall of retrieval practice strategy. (a) Mediation model in the immediate recall conditioning. (b) Mediation model in the delayed recall conditioning. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$

ARC score was significantly higher for Retrieval practice ( $M = 0.56$ ,  $SD = 0.04$ ) compared to Restudy ( $M = 0.32$ ,  $SD = 0.03$ ),  $p < 0.001$ ,  $d = 6.78$ , 95% CI [0.15, 0.31]. Within the Sham group, ARC score was significantly higher for Retrieval practice ( $M = 0.37$ ,  $SD = 0.04$ ) compared to Restudy ( $M = 0.27$ ,  $SD = 0.03$ ),  $p < 0.05$ ,  $d = 2.82$ , 95% CI [0.01, 0.18].

In the delayed recall (Fig. 3B), a significant interaction effect was found between stimulation type and learning strategy  $F(1,50) = 8.121$ ,  $p < 0.01$ ,  $\eta_p^2 = 0.140$ . Within the Anodal group, ARC score was significantly higher for Retrieval practice ( $M = 0.48$ ,  $SD = 0.03$ ) compared to Restudy ( $M = 0.24$ ,  $SD = 0.02$ ),  $p < 0.001$ ,  $d = 9.41$ , 95% CI [0.16, 0.31]. Within the Sham group, the ARC score was not significantly different for retrieval practice ( $M = 0.30$ ,  $SD = 0.04$ ) compared to restudy ( $M = 0.22$ ,  $SD = 0.02$ ),  $p = 0.056$ ,  $d = 2.52$ , 95% CI [-0.00, 0.16].

#### Mediation analysis

Retrieval practice strategy in the immediate recall conditioning (Fig. 4a), bootstrap analyses showed that the indirect effect of the mediator test did not contain 0 ( $Effect = 0.153$ ,  $SE = 0.047$ , 95% CI = [0.060, 0.245]), accounting for 96.36% of the total effect. Additionally, after controlling for the mediating variable, ARC score, the direct effect of the independent variable (stimulation type) on the dependent variable (correct recall of retrieval practice) is not significant with an interval containing 0 ( $Effect = 0.005$ ,  $SE = 0.007$ , 95% CI = [-0.008, 0.020]), suggesting that, in the effect of stimulation type on the rate of correct recall of retrieval practice on the immediate recall, the ARC score had a mediating effect. In addition, no mediation effect was found in the immediate test of the restudy strategy, bootstrap analyses showed that the indirect effect of the mediator test contained 0 ( $Effect = 0.048$ ,  $SE = 0.045$ , 95% CI = [-0.038, 0.138]).

Retrieval practice strategy in the delayed recall conditioning (Fig. 4b), bootstrap analyses showed that the

indirect effect of the mediation test did not contain 0 ( $Effect=0.156$ ,  $SE=0.045$ , 95% CI = [0.070, 0.247]), accounting for 96.87% of the total effect. In addition, after controlling for the mediating variable, ARC score, the direct effect of the independent variable (stimulation type), on the dependent variable (correct recall of retrieval practice) is not significant with an interval containing 0 ( $Effect=0.005$ ,  $SE=0.004$ , 95% CI = [-0.003, 0.013]), suggesting that, in the effect of stimulation type on the rate of correct recall of retrieval practice in the delayed recall condition, ARC score also had a mediating effect. Similarly, no mediating effect was found in the delay test of restudy strategy, bootstrap analyses showed that the indirect effect of the mediator test contained 0 ( $Effect=0.017$ ,  $SE=0.031$ , 95% CI = [-0.043, 0.080]).

## Discussion

This study is the first to combine continuous periodic tDCS with retrieval practice strategy, exploring its additive effect on the maintenance of semantic memory in patients with schizophrenia. The results indicate that in the semantic memory learning of patients with schizophrenia, anodal tDCS stimulation can effectively enhance the maintenance of semantic memory and improve memory organization compared to sham stimulation. Furthermore, robust retrieval practice effects were observed [28], with significantly higher correct recall rates in the retrieval practice condition compared to the restudy condition, with a large effect size. ARC scores were found to fully mediate the role of stimulus type and final correct recall in retrieval practice strategy list learning, whereas this role was not found in restudy strategy list learning. This is further supported by the fact that the combination of the two strategies resulted in a synergistic memory enhancement effect, compensating for the previous situation where the effect of tDCS was offset by the retrieval practice effect when used alone [40].

Retrieval practice enhances the global efficiency of memory-related network connectivity [51]. It consolidates long-term memory through dynamic changes in the functional brain network patterns centered on the ventrolateral prefrontal cortex (VLPFC)-posterior parietal cortex (PPC) and DLPFC-medial temporal lobe (MTL, particularly the hippocampus). In contrast, restudy results in more distinct sensory features encoded in the visual cortex for the studied words, reducing neural overlap in semantic representations of the left temporal pole and modulating the memory strength between encoding and retrieval [52]. Moreover, restudy enhanced the memory strength between encoding and retrieval in the visuospatial cortex but reduced it in the frontal cortex [53].

Impaired neuroplasticity and impaired GABA and glutamate neurotransmission in patients with schizophrenia

[16]. Ten sessions of tDCS over five days may enhance GABA-mediated inhibition and amplify the magnitude of long-term potentiation (LTP) [54, 55]. Immediately after the tenth tDCS stimulation in the immediate test, the excitability of the L-DLPFC was higher. Coincidentally, the prefrontal cortex is capable of greater activation during retrieval practice than during restudy [35], so memory performance was better for the retrieval practice strategy. In delayed tests, prior tDCS treatment effectively regulates neurotransmitter levels in individuals with schizophrenia, facilitating the transmission of relevant information and suppression of irrelevant signals. Given that retrieval practice establishes more robust synaptic memory traces than restudy [56], patients in the anodal stimulation group continue to exhibit superior memory performance.

Previous studies have shown that repeated exposure to category words does not enhance clustering during subsequent recall, whereas retrieval practice significantly promotes clustering [57]. This finding aligns with the present study, where the ARC clustering scores in the retrieval practice strategy were significantly higher than those in restudy. Moreover, only in the retrieval practice condition was ARC clustering scores found to fully mediate the relationship between stimulus type and recall rate. This indicates that tDCS does not directly affect recall performance under retrieval practice but exerts its influence by enhancing semantic clustering organization, which in turn impacts semantic memory performance. tDCS likely enhances the regulation of neurotransmitter levels, facilitating the transmission of relevant information while suppressing irrelevant information. The ARC clustering scores, which organizes semantic information based on category relevance, reflects this process. By promoting the retrieval of semantically related information and inhibiting errors from irrelevant semantic information, tDCS complements the effects of retrieval practice. Furthermore, the use of retrieval practice strategy helps the fine-grained processing of semantic representation and promotes the perfection of clustering organization [34].

More stable tDCS stimulation of the L-DLPFC was found in patients with schizophrenia under a retrieval practice strategy. Successive cycles of tDCS can promote the retention of patients' semantic memory by improving their semantic clustering organization, validating the theoretically derived improvement of semantic network organization by tDCS intervention in the L-DLPFC in previous studies [58, 59]. Moreover, when combined with retrieval practice, tDCS exhibited an additive effect [60]. Schizophrenia patients exhibit cognitive deficits not only in terms of intelligence but also in their ability to use strategies, and tDCS has an immediate improvement effect on strategy use in these patients [61]. The DLPFC



is the main affected area in high cognitive demand relational encoding [30]. During encoding and retrieval processes in schizophrenia patients, DLPFC activation is disrupted, while the VLPFC remains intact during item encoding [62]. Therefore, it is believed that DLPFC provides control over relational encoding, and anodal tDCS can facilitate the refinement of semantic memory organization and improve the use of strategies, thus improving their semantic memory performance.

The absence of a healthy control group represents a notable limitation of this study. We considered the potential ceiling effects of transcranial direct current stimulation (tDCS) and semantic memory tests in healthy individuals [63]. In comparison with prior research, the semantic recall rates in patients with schizophrenia remain consistently lower than those of healthy individuals and older adults [23, 40, 64]. This suggests that tDCS alone may not be sufficient to restore semantic memory to the levels observed in healthy individuals. However, the findings of this study indicate that the combination of tDCS and cognitive strategies shows promise in improving cognitive function in patients with schizophrenia. Whether this approach can enable patients to achieve cognitive performance comparable to that of healthy individuals remains a critical question for future research.

Furthermore, our study did not directly investigate the mechanisms underlying the effects of tDCS and retrieval practice strategies in individuals with schizophrenia. Future investigations could integrate brain-computer interface (BCI) devices, such as eego™ rt, to collect real-time EEG data during tDCS interventions, allowing for a more detailed exploration of brainwave alterations in this patient population. Lastly, enhancing the clinical relevance of experimental studies using noninvasive brain stimulation and cognitive strategies is an essential consideration. Future research should aim to improve not only cognitive function but also the quality of life and social functioning of patients with schizophrenia through the combined use of tDCS and learning strategies [65].

In summary, the synergistic effect of combining tDCS, a portable and safe neuroregulatory method, with retrieval practice, a simple yet effective behavioral technique, is significantly underestimated. Future research endeavors should focus on further exploration and integration of diverse intervention methods, such as learning strategies and cognitive behavioral training, to enhance the treatment and rehabilitation of schizophrenia patients.

## Conclusions

In this study, we found that (1) both tDCS and retrieval practice can effectively promote the maintenance and improvement of semantic memory in patients with schizophrenia. (2) Continuous periodic tDCS can amplify

the effect of retrieval practice to a certain extent. Specifically, anodal tDCS combined with retrieval practice can better assist patients with schizophrenia in improving the maintenance of semantic memory and the refinement of memory organization.

## Abbreviations

tDCS	Transcranial direct current stimulation
L-DLPFC	Left dorsolateral prefrontal cortex
VLPFC	Ventrolateral prefrontal cortex
RP	Retrieval practice
RS	Restudy
ARC	Adjusted Ratio of Clustering
BCI	Brain-computer interface
GABA	γ-aminobutyric acid
NMDA	N-methyl-D-aspartate
EEG	Electroencephalogram

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12888-025-06530-y>.

Supplementary Material 1

## Author contributions

W.P. participated in methodology, investigation, conceptualization, data curation, writing - original draft and writing - review & editing. T.L. participated in software, data curation, investigation and writing - original draft. X.M. participated in validation, project administration, funding acquisition, resources, supervision, writing - original draft and writing - review & editing. X.H. participated in resources and supervision.

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## Data availability

Availability of dataData from this study are available: <https://data.mendeley.com/preview/bz4k2xgdwy? a=53798262-f8c1-45d5-ad7e-2633f9f4bdf3>.

## Declarations

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

### Ethical approval and consent to participate

The trial was approved by the Ethics Committee of Lanzhou Third People's Hospital and the School of Psychology at Northwest Normal University (No.2023023) and all methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all participants. Patients were informed that their participation was a voluntary activity and that they had the right to leave the study at any time with no negative effect on their treatment. The present trial has been registered in the American Registry of Clinical Trials Center (ID: NCT06538259) [<http://clinicaltrials.gov/>](Retrospectively Registered Date: 08/03/2024).

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