Unique Protocol ID: No.2023025

Official Title: Effects of transcranial electrical stimulation combined with retrieval practice on semantic memory in patients with schizophrenia

Document Title: Study Protocol

Date of the Document: 2024/08/03

Study Protocol

Effects of transcranial electrical stimulation combined with retrieval practice on semantic memory in patients with schizophrenia

1. Introduction

Research on semantic memory in schizophrenia patients has revealed weaker activation in the prefrontal cortex, potentially linked to cognitive impairments [1,2]. Prior studies have suggested that continuous periodic tES intervention in the left dorsolateral prefrontal cortex (L-DLPFC) can enhance semantic recognition abilities [3]. Semantic memory organization in schizophrenia patients approaches that of healthy individuals after undergoing continuous tES stimulation of the left DLPFC for five days, ten times [4]. Thus, stimulating the excitability of the L-DLPFC through tES 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 [5]. 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 tES [6]. This suggests that there is consistency in brain activation between tES and retrieval practice, and combining the two may result in mutually reinforcing effects.

A study involving 119 healthy subjects investigated the combination of tES intervention with retrieval practice and found that the strong retrieval practice effect left no room for tES to improve memory performance[7]. The combination of single-session online tES with retrieval practice in healthy individuals and found that the memory performance of anodal stimulation was inferior to cathodal stimulation and sham stimulation [8]. We have already explored the role of continuous periodic tES combined with interim testing on spatial route learning in patients with schizophrenia in a previous study [9], and found that both the learning strategy and tES independently facilitated the ability of patients with schizophrenia to learn new information in spatial route learning, suggesting that the tES of L-DLPFC has a significant improvement effect. In contrast, targeted tES treatment may be more effective for memory-impaired populations such as schizophrenia [10]. Therefore, further investigation is needed to determine the effectiveness of combining tES and retrieval practice for semantic memory intervention in schizophrenia patients. From a theoretical perspective, this combination may have a dual activation effect because (1) tES 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 tES, thereby producing a synergistic effect.

Therefore, this study aims to investigate whether combining tDCS, tACS with retrieval practice facilitates the maintenance of semantic memory and improvement of semantic organization by comparing the use of retrieval practice strategies in patients receiving anodal L-DLPFC stimulation, sham stimulation.

2. Methods

2.1 Participants

60 schizophrenic patients plan to be recruited from the mental health center. All patients must sign an informed consent form.

Patients with schizophrenia are diagnosed and assessed by two chief psychiatrists. Neuropsychological background tests included the Montreal Cognitive Assessment (MoCA)[11] for general cognitive function and the Positive and Negative Syndrome Scale (PANSS)[12]. A parallel-group, single-blind study design was used to assign subjects to the two stimulus types using a stratified randomization method based on baseline Montreal Cognitive Assessment performance. 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; (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.

2.2 Design

A mixed experimental design of 3 (Stimulation type: tES stimulation, tACS stimulation, sham stimulation) × 2 (Learning strategy: retrieval practice, restudy) × 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.

2.3 Devices and Materials

2.3.1 Devices

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

2.3.2 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 [13].

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), $t(19) = -1.765$, $p = .094$, 95% CI [-0.41, 0.03], $t(19) = 1.344$, $p = .195$, 95% CI [-0.05, 0.25].

2.4 Procedure

Treatment is administered by two examiners, each patient receives transcranial electrical stimulation with simultaneous learning of word lists. 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 **Figure 1**).

(1) Stimulation phase

In the tDCS 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 2mA was applied for 20 minutes during each stimulation session. In the tACS group, the anode was placed in the F3 region of the left dorsolateral prefrontal cortex (DLPFC), and the cathode was placed in the right supraorbital region (Fp2), and the current used was 2 mA AC at 40 Hz, with a stimulation time of 20 min. 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 before and after stimulation, patients were unaware that the current was turned off.

(2) Learning phase

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

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 seconds, 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 minutes. 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).

(3) Testing phase

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

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

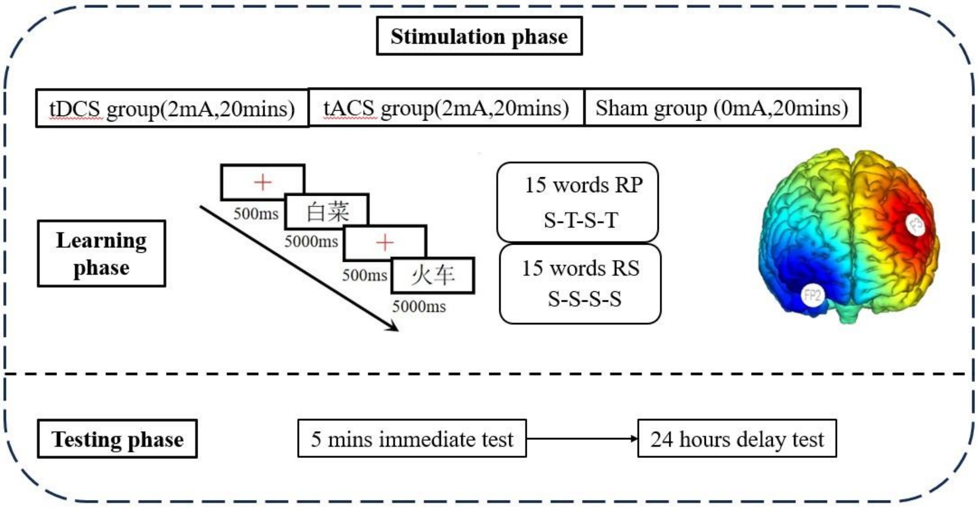

Figure 1. Experiment procedure.

2.5 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 [14,15]. ARC scores range from 1 to 1. A 0 score indicates a level of clustering similar to what would be expected by chance, and a score of 1 implies perfect clustering. Negative values of ARC scores mean atypical and uninterpretable recall patterns[16]. 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 (η_p^2; ANOVAs).

Study Status

Record Verification: August 2024

Overall Status: Not yet recruiting

Study Start: August 12, 2024 [Anticipated]

Primary Completion: September 15, 2024 [Anticipated]

Study Completion: September 20, 2024 [Anticipated]

List of abbreviations

tES transcranial electrical stimulation

L-DLPFC left dorsolateral prefrontal cortex

VLPFC ventrolateral prefrontal cortex

ARC Adjusted Ratio of Clustering

References

[1] Koike S, Takizawa R, Nishimura Y, Kinou M, Kawasaki S, Kasai K. Reduced but broader prefrontal activity in patients with schizophrenia during n-back working memory tasks: A multi-channel near-infrared spectroscopy study. J Psychiatr Res 2013;47:1240–6. https://doi.org/10.1016/j.jpsychires.2013.05.009.

[2] Marumo K, Takizawa R, Kinou M, Kawasaki S, Kawakubo Y, Fukuda M, et al. Functional abnormalities in the left ventrolateral prefrontal cortex during a semantic fluency task, and their association with thought disorder in patients with schizophrenia. NeuroImage 2014;85:518–26. https://doi.org/10.1016/j.neuroimage.2013.04.050.

[3] Imperio CM, Chua EF. Differential effects of remotely supervised transcranial direct current stimulation on recognition memory depending on task order. Front Hum Neurosci 2023;17:1239126. https://doi.org/10.3389/fnhum.2023.1239126.

[4] Sumiyoshi C, Narita Z, Inagawa T, Yamada Y, Sueyoshi K, Hasegawa Y, et al. Facilitative Effects of Transcranial Direct Current Stimulation on Semantic Memory Examined by Text-Mining Analysis in Patients With Schizophrenia. Front Neurol 2021;12:583027. https://doi.org/10.3389/fneur.2021.583027.

[5] Jantzi C, Mengin AC, Serfaty D, Bacon E, Elowe J, Severac F, et al. Retrieval practice improves memory in patients with schizophrenia: new perspectives for cognitive remediation. BMC Psychiatry 2019;19:355. https://doi.org/10.1186/s12888-019-2341-y.

[6] Zhang L, Jiang Y, Zhang J. The Facilitating Effect of Retrieval Difficulty on the Retrieval Practice Effect for Difficult Materials: Evidence from Behavior and fNI RS. 25th Natl. Acad. Conf. Psychol., Chinese Psychological Society; 2023, p. 3. https://doi.org/10.26914/c.cnkihy.2023.057280.

[7] Cavendish BA, de Lima MFR, Perícoli L, Buratto LG. Effects of combining retri eval practice and tES over long-term memory: A randomized controlled trial. Brai n Cogn 2022;156:105807. https://doi.org/10.1016/j.bandc.2021.105807.

[8] Brunyé TT, Smith AM, Horner CB, Thomas AK. Verbal long-term memory is en hanced by retrieval practice but impaired by prefrontal direct current stimulation. Brain Cogn 2018;128:80–8. https://doi.org/10.1016/j.bandc.2018.09.008.

[9] Li T, Ma X, Pan W, Huo X. The impact of transcranial direct current stimulatio n combined with interim testing on spatial route learning in patients with schizop hrenia. J Psychiatr Res 2024;177:169–76. https://doi.org/10.1016/j.jpsychires.2024.0 7.016.

[10] Dedoncker J, Brunoni AR, Baeken C, Vanderhasselt M-A. A Systematic Review and Meta-Analysis of the Effects of Transcranial Direct Current Stimulation (tES) Over the Dorsolateral Prefrontal Cortex in Healthy and Neuropsychiatric Samples: Influence of Stimulation Parameters. Brain Stimulat 2016;9:501–17. https://doi.org/ 10.1016/j.brs.2016.04.006.

[11] Mahendran R, Chua J, Feng L, Kua EH, Preedy VR. Chapter 109 - The Mini-M ental State Examination and Other Neuropsychological Assessment Tools for Dete

cting Cognitive Decline. In: Martin CR, Preedy VR, editors. Diet Nutr. Dement. Cogn. Decline, San Diego: Academic Press; 2015, p. 1159–74. https://doi.org/10.1016/B978-0-12-407824-6.00109-9.

[12] Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–76. https://doi.org/10.1093/schbul/13.2.261.

[13] Bordignon S, Zibetti MR, Trentini CM, Resende AC, Minervino CASM, Silva-Filho JHD, et al. Normas de associação semântica para 20 categorias em adultos e idosos. Psico-USF 2015;20:97–108. https://doi.org/10.1590/1413-82712015200109.

[14] Ma X, Li T, Li Z, Zhou A. Episodic context reinstatement promotes memory retention in older but not younger elementary schoolchildren. Br J Dev Psychol 2020;38:304–18. https://doi.org/10.1111/bjdp.12321.

[15] Roenker DL, Thompson CP, Brown SC. Comparison of measures for the estimation of clustering in free recall. Psychol Bull 1971;76:45–8. https://doi.org/10.1037/h0031355.

[16] Kahana MJ, Howard MW, Polyn SM. Associative Retrieval Processes in Episodic Memory. Learn. Mem. Compr. Ref., Elsevier; 2008, p. 1–24. https://doi.org/10.1016/B978-012370509-9.00185-6.