Synergistic Treatment of Negative Symptoms and Cognitive Function Deficits in Long-Term Hospitalized Schizophrenia Patients Using tACS

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1. Research Background

Schizophrenia is a complex mental disorder, typically characterized by cognitive dysfunction, emotional flatness, hallucinations, and delusions. Although antipsychotic medications are the primary treatment method for schizophrenia, they have limited effectiveness in improving cognitive deficits and negative symptoms. Moreover, pharmacological treatment may be accompanied by various side effects. Therefore, finding more effective treatment strategies is crucial.

Transcranial alternating current stimulation (tACS), as an emerging non-invasive brain stimulation technique, influences neural network function by modulating brain electrical activity, thus showing promising prospects in the treatment of mental disorders. Research indicates that tACS can enhance neuroplasticity in specific brain regions, thereby improving cognitive function and emotional states. For example, studies on depression patients have found that tACS can effectively improve mood and significantly reduce the severity of depressive symptoms[1]. Furthermore, tACS is believed to have potential benefits for treating anxiety and schizophrenia, with related research continuously increasing[2].

The working principle of tACS primarily involves applying low-intensity alternating current to regulate neuronal firing patterns, thereby achieving precise control of brain activity. Compared to traditional transcranial magnetic stimulation, tACS has greater advantages in stimulation depth and targeting, allowing more effective influence on deep brain region activities, which is particularly important for treating some treatment-resistant mental disorders[3]. For instance, recent research suggests that tACS can effectively improve cognitive function and negative symptoms in schizophrenia patients, providing new insights into the application of this technology in mental disorder treatment[4].

Although tACS shows promising prospects in clinical applications, more randomized

controlled trials are needed to verify its safety and effectiveness. The existing studies have relatively small sample sizes and mostly focus on short-term effect assessments, lacking systematic research on long-term effects [5]. Moreover, individual differences may play an important role in the therapeutic effects of tACS, so future research needs to pay more attention to developing personalized treatment plans to achieve better therapeutic outcomes [6].

Eye-tracking technology has become a key tool for exploring human cognitive processes in psychological research, based on the "eye-mind hypothesis"—that visual attention allocation directly reflects underlying cognitive processing. Currently, this technology provides researchers with objective indicators of cognitive activities by precisely recording parameters such as fixation point distribution, dwell time, and saccadic paths. In cognitive psychology, eye movement data reveals information processing strategies in tasks like reading, visual search, and problem-solving; in developmental psychology, eye tracking helps researchers understand cognitive developmental trajectories of infants and young children; social psychology uses this technology to explore facial expression recognition and attention allocation patterns in social interactions; clinical psychology considers characteristic eye movement abnormalities as potential biomarkers for various psychological disorders. This multidisciplinary application not only enriches theoretical construction but also provides scientific basis for practical applications, such as developing auxiliary diagnostic tools, assessing treatment effects, and designing human-machine interactions. The non-invasive nature and increasingly improved portability of eye tracking make it an ideal bridge connecting subjective experiences with objective measurements. Therefore, it is also expected to serve as an important biomarker for measuring negative symptoms and cognitive deficits in schizophrenia.

Research indicates that cognitive function impairment in schizophrenia patients may be closely related to elevated levels of peripheral inflammatory cytokines. Significantly increased levels of IL-6, IL-1β, TNF-α, and C-reactive protein (CRP)

are closely associated with decreased performance in cognitive domains such as attention, executive function, working memory, verbal, and visual learning [7]. Additionally, studies on first-episode psychosis patients found that levels of TNF-α, IFN-γ, IL-1β, and IL-12 were negatively correlated with cognitive impairments in sustained attention, verbal learning, and executive functions [8]. In summary, inflammatory responses may play a crucial role in cognitive impairment in schizophrenia. Therefore, regularly monitoring serum levels of inflammatory cytokines such as IL-1β, IFN-γ, IL-6, and IL-10 has important clinical significance for early assessment and intervention of patient cognitive function.

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2. Research Objectives and Expected Results

2.1. Research Objectives

This study aims to investigate the augmented therapeutic effect of tACS on negative symptoms and cognitive function in long-term hospitalized patients with schizophrenia; Using event-related brain electrical activity induced by emotional stimuli in virtual reality scenarios as a biomarker, analyze its correlation with the clinical efficacy of tACS.

2.2. Expected Outcomes

Confirm that tACS can improve negative symptoms and cognitive function in long-term hospitalized schizophrenia patients; Predict the therapeutic effect of tACS on improving negative symptoms and cognitive function in long-term hospitalized schizophrenia patients through biomarkers, guiding precise clinical application.

3. Research Content and Methods

3.1. Research Content

This study aims to investigate the augmentative therapeutic effect of transcranial alternating current stimulation (tACS) on negative symptoms and cognitive function in long-term hospitalized patients with schizophrenia; and to use emotion-induced event-related brain electrical activities under virtual reality scenarios as objective biomarkers for schizophrenia, analyzing their predictive value for the clinical efficacy of tACS.

A case-control experiment comparing the differences in emotion-induced event-related brain electrical activities, eye movements, and serum inflammatory factors between 60 long-term hospitalized schizophrenia patients and 30 healthy controls under virtual reality scenarios.

A randomized controlled experiment comparing the therapeutic effects on negative symptoms and cognitive function between the 30 tACS group and the 30 sham stimulation group of long-term hospitalized schizophrenia patients. Additionally, analyzing the relationship between treatment efficacy and baseline and post-treatment brain electrical biomarkers, susceptibility genes, and serum inflammatory factors.

3.2. Research Methods

Subject Recruitment: This study plans to recruit 60 long-term hospitalized schizophrenia patients from the hospital's outpatient and inpatient departments, and 30 normal controls from the community. All participants will sign an informed consent form before the study begins and obtain ethical approval for participation, ensuring

Intervention Protocol: The intervention will last 20 days, with two tACS stimulations per day, each lasting 40 minutes, using a current of 15mA. The tACS intervention group will receive real electrical stimulation, while the sham stimulation group will receive placebo stimulation (without current).

Clinical Assessment: Using standardized clinical assessment tools, evaluate the negative symptoms (SANS, CAINS, BNSS) and cognitive functions (MCCB, including attention, executive function, visual memory, declarative memory, working memory, alertness, information processing speed, and social cognition) of schizophrenia patients.

Tolerability and Safety Assessment: Using a custom questionnaire to monitor patient discomfort and any side effects during tACS stimulation intervention to evaluate the safety and tolerability of the method.

Biomarker Detection: Monitor subjects' emotion-induced brain electrical activity as an objective biomarker for schizophrenia (high-frequency oscillation power in the prefrontal cortex, functional connectivity between PFC and somatosensory cortex, visual cortex) through EEG under virtual reality conditions. Track subjects' saccadic amplitude and direction through eye movement analysis, measuring subjects' gaze time when viewing specific stimuli (such as emotional faces or social scenes), and assess the scanning trajectory length in visual exploration tasks. Explore the effects of tACS stimulation on brain electrical activity. After cognitive assessment, 2ml of venous blood will be extracted and stored at -80° C for testing. Periodically detect serum inflammatory cytokines (IL1β, IFN-γ, IL6, IL10, etc.) and schizophrenia susceptibility genes (GAD1, GABAA, GRM3, etc.).

Data Analysis: Using ANOVA to compare differences in baseline indicators between patient and normal control groups; using repeated measures ANOVA to compare differences in changes of negative symptom scales, cognitive measurement indicators, EEG indicators, serum factors, etc. between tACS intervention and sham stimulation groups. Using Pearson correlation analysis to explore the correlation between clinical

indicator improvements and biomarker changes.

4. Risks and Side Effects

This study will collect blood samples from patients and normal controls. Patients will receive intervention with commercially available medical device alternating current stimulation. The potential risks of these measures are small, known to include fainting caused by blood drawing, dizziness caused by alternating current stimulation, but these are generally mild and controllable. A very small number of individuals may also potentially have other unknown risks.

5. Withdrawal Conditions

Patient death

Patient actively withdraws from the study;

The research physician determines that the patient is not suitable to continue participating in the study,

Other reasons.

6. Product Introduction

The tACS device and electrodes were provided by Nexalin Technology, Inc. (CA, USA). The device is FDA and NMPA approved for clinical use in psychiatric patients (501K=K024377, stimulator, transcranial electrical treatment, CFR 882.5800, US Patent #6904322B2). The treatment was administered through 3 dedicated Nexalin electrodes, placed on the frontal lobe (corresponding to the Fp1, Fpz, Fp2 regions in the international 10-20 system EEG electrode placement, with electrode sizes of 4.45 cm×9.53 cm), one electrode on the forehead and two electrodes on the bilateral mastoids (electrode sizes 3.18 cm×3.81 cm), with one electrode on each mastoid.

Currently, the device has been used for treatment in multiple hospitals including Beijing Anding Hospital and Xuanwu Hospital, with published articles (Preliminary exploration of transcranial alternating current stimulation effectiveness in treatment-naive depression patients, and the efficacy and safety of transcranial alternating current stimulation combined with antidepressant drugs in depressive episodes)

7. Conflict of Interest

This study has no relevant conflicts of interest.

8. Privacy and Confidentiality

This study will implement a strict privacy protection policy. All information related to this project and its collaboration will be carefully managed, and no personally identifiable information about the participants will be disclosed to anyone outside this institution under any circumstances. Even if the research results are published, the participants' personal information will not be revealed.

Participants have the right to know the final research results. Their personal information will be protected during the entire process of data collection, storage, and use (including analysis and comparison).

Principal Investigator's Signature:

Long-term Hospitalized Schizophrenia Patient Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Diagnosed with schizophrenia according to DSM-5 and hospitalized continuously for more than six months

2. Age between 18 and 65 years old

3.Willing to participate in the study and sign the informed consent form

4.Stable condition, with minimal change (less than 15%) in total PANSS score in the two months prior to the study

5.Education level of primary school or above

6.Normal vision or correctable to normal

Exclusion Criteria:

1. Comorbid diagnoses of other mental disorders according to DSM-5

2. History of severe neurological diseases, epilepsy, or craniocerebral trauma

3. Presence of severe organic diseases with unstable vital organ functions (such as heart, liver, or kidney)

4. Infectious skin disease

5. Concomitant use of other drugs that may affect the results during the study, such as benzodiazepines, non-benzodiazepine sedatives, and psychostimulants

6. Pregnant or lactating women

7. Patients with claustrophobia

8. Those with a history of alcohol or drug abuse

9. Those who have previously received ineffective or intolerable TACS treatment

Normal Control Group Inclusion and Exclusion Criteria

Inclusion Criteria:

1. No previously diagnosed mental illness

2. Age between 18 and 65 years old

3. Willing to participate in the research and sign the informed consent form

4. Education level of elementary school or above

5. Normal vision or corrected to normal vision

6. Residents living in the Pudong community

Exclusion Criteria:

1. History of severe neurological diseases, such as epilepsy, history of craniocerebral trauma, etc.

2. Those with severe organic diseases of vital organs such as heart, liver, and kidney that are unstable

3. Those with infectious skin diseases

4. Concurrent use of drugs during the study that may affect the results, such as benzodiazepines, non-benzodiazepine sedatives, and psychostimulants

5. Pregnant or lactating women

6. Patients with claustrophobia

7. Individuals with a history of alcohol or substance abuse