RESEARCH ARTICLE

The impact and therapeutic effects of transcranial electrical stimulation (tES) on cognitive function in patients with Schizophrenia, considering lipid metabolism

Zhang Cheng*

Bozhou University, Traditional Chinese Medicine College, Bozhou, Anhui, China.

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Cognitive impairment and metabolic disorders are common in patients with schizophrenia, but the regulatory role of lipid metabolism in the efficacy of neuromodulatory treatments remains to be elucidated. This study investigated the link between lipid metabolism and cognitive decline in schizophrenia patients, assessed the effectiveness of transcranial electrical stimulation in improving cognitive function, and tested the predictive value of baseline blood lipid levels on the efficacy of transcranial electrical stimulation. A randomized double-blind pseudo stimulation control design was used to randomly group 80 patients with schizophrenia with 40 patients in each group for a 2-week transcranial electrical stimulation intervention. Data was collected using the MATRICS consensus cognitive test and blood lipid testing for statistical analysis. The results demonstrated a significant positive correlation between the baseline period and speech learning (r = 0.283), as well as a significant negative correlation between triglyceride levels and working memory performance (r = -0.248). Compared with the sham stimulation group, real transcranial electrical stimulation intervention significantly improved working memory. Regression analysis confirmed that baseline high-density lipoprotein cholesterol positively predicted improvement in speech learning (β = 0.412), while triglycerides negatively predicted improvement in working memory (β = -0.379). Lipid metabolism was associated with cognitive impairment in schizophrenia. Transcranial electrical stimulation could effectively improve cognition, and its efficacy was regulated by baseline blood lipid levels. Blood lipid indicators could serve as potential biomarkers for predicting the efficacy of transcranial electrical stimulation, suggesting that metabolic intervention could optimize neural regulation strategies and provide new evidence for personalized neural regulation therapy.

Keywords: Schizophrenia; transcranial electrical stimulation; cognitive function; blood lipids; high density lipoprotein.

***Corresponding author:** Zhang Cheng, Bozhou University, Traditional Chinese Medicine College, Bozhou, Anhui 236800, China. Email: cz448789@163.com.

Introduction

Schizophrenia (SZ) represents a serious mental health condition marked by a high rate of disability, presenting with both positive and negative manifestations, in conjunction with widespread cognitive deficits [1]. Cognitive impairment involves multiple dimensions such as working memory, executive function, and cognitive processing velocity, and is a key factor affecting patients' social and occupational functioning as well as long-term prognosis [2]. The commonly used first- and second-generation antipsychotic drugs can alleviate positive symptoms, but their cognitive improvement effect is limited, and some may also have

metabolic side effects [3]. Therefore, developing non-pharmacological interventions for cognitive impairment has become an urgent problem that needs to be overcome. Additionally, an increasingly concerned clinical phenomenon is the metabolic syndrome in SZ, especially the high incidence rate of dyslipidemia [4]. This high comorbidity risk is believed to be the result of multiple factors working together including possible endocrine and metabolic dysregulation of the disease itself, as well as unhealthy lifestyles such as high calorie diets and lack of exercise. The use of second-generation antipsychotic drugs is also recognized as an important iatrogenic factor leading to weight gain and dyslipidemia [5].

The association between dyslipidemia and cognitive function (CF) is not accidental. From a biological perspective, lipids are the cornerstone of the central nervous system. Valenza *et al*. suggested that cholesterol was a key maintainer of neuronal cell membrane fluidity and integrity, directly affecting ion channel function and signal transduction [6]. Galkina *et al*. stated that fatty acids, especially polyunsaturated fatty acids, not only participated in synaptic plasticity, but were also the main components of myelin sheath, and the integrity of myelin sheath determined the speed and efficiency of nerve impulse transmission [7]. In addition, abnormal lipid metabolism may also cause damage to neurons by exacerbating neuroinflammatory reactions, oxidative stress, and other pathways. Dyslipidemia in patients with SZ may exacerbate patients' cognitive impairment through direct or indirect neurobiological pathways [8]. In the context of seeking new cognitive intervention methods, as a non-invasive, secure, and easily tolerated neural regulation technique, transcranial electrical stimulation (tES), especially transcranial direct current stimulation (tDCS), showed great potential for application [9]. tDCS regulates cortical excitability in specific brain regions by placing electrodes on the scalp and applying weak direct current, thereby inducing changes in neural plasticity. Multiple research investigations have confirmed that tDCS can effectively boost cognitive abilities in both healthy individuals and those suffering from various neurological and psychiatric disorders [10]. In recent years, research on SZ also shows that anodic tDCS targeting the left dorsolateral prefrontal cortex (L-DLPFC), a cognitive control core brain area, can exert a beneficial improvement impact on patients' working memory, executive function, *etc*. [11].

However, previous studies have mainly investigated the therapeutic effects of tES and metabolic status in isolation, leaving the interaction between lipid metabolism and tES efficacy unexplored. This study investigated the regulatory role of baseline lipid metabolism in tES-induced cognitive improvement using a randomized, double-blind, sham-controlled trial, which included 80 patients with SZ and utilized tES targeting the left dorsolateral prefrontal cortex (L-DLPFC). The results of this study would identify predictive metabolic biomarkers, thereby optimize neural regulation strategies and provide evidence for personalized cognitive interventions.

Materials and methods

Research subject and grouping

A total of 80 participants including 44 males and 36 females, aged from 18 to 55 years old, diagnosed with SZ were recruited from the SZ outpatient and inpatient of the Nanjing Mental Health Center (Nanjing, Jiangsu, China) between January 2023 and June 2024 with the inclusion criteria of meeting the DSM-5 diagnostic criteria (American Psychiatric Association, Arlington, VA, USA) [12], in the stable condition and stable dosage of antipsychotic drugs in the past 3 months, right handed and with a junior high school education or above. The exclusion criteria were presence of tES related contraindications such as intracranial metal implants and history of epilepsy, having significant physical illnesses, neurological disorders, or other major mental disorders affecting central nervous system function or lipid metabolism, having history of

substance abuse in the past 6 months, pregnant or lactating women. The participants were randomly allocated into active tES stimulation group with 23 males and 17 females, average age of 34.82 ± 8.13 years old, 12.31 ± 2.58 years of education and the sham stimulation group with 21 males and 19 females, average age of 35.61 ± 7.94 years old, 12.74 ± 2.66 years of education [13]. All procedures of this research were approved by the Ethics Committee of Bozhou University (Bozhou, Anhui, China) (Approval No. 24223). The written informed consent forms were obtained from all participants and their guardians.

Intervention and assessments

The intervention protocol followed the international 10 - 20 electrode placement system (Beckman Coulter Inc., Brea, CA, USA) and used NeuroConn DC-STIMULATOR MC (Neurocare group AG, Munich, Germany) with the anode positioned over the L-DLPFC (F3) and the cathode over the right supraorbital area (Fp2). For the active tES group, a continuous current of 2 mA was applied for 20 minutes to induce effective neuromodulation, while, in the sham tES group, the current was ramped up to 2 mA only for the initial and final 30 seconds of the 20 minutes session with no stimulation delivered in the intervening period to simulate somatic sensations and serve as a placebo control [14]. Functionally, the electrical current flew from the anode towards the cathode, inducing neural excitation in the cortical region beneath the anode while exerting inhibitory effects in the region under the cathode. To ensure double blinding, the sham condition utilized identical electrode placement but employed an adjusted current output mode to simulate stimulation sensations without therapeutic effect. The comprehensive baseline assessments (T0) of all participants were conducted, which included the collection of demographic data (age, gender, education years), clinical data (disease duration, drug type, and equivalent chlorpromazine dose), and fasting blood lipid levels by using the positive and negative syndrome scale (PANSS) (Multi-Health Systems Inc., Toronto, ON, Canada) to assess the severity of psychiatric symptoms [15], the MATRICS consensus cognitive battery (MCCB) (MATRICS Assessment Inc., Los Angeles, CA, USA) to assess CF [16], and fasting venous blood samples to measure total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels using a fully automated biochemical analyzer prior to the intervention trials. The intervention was administered once daily, 5 days per week, over a 2-week period with a total of 10 sessions. Each session consisted of 20 minutes of stimulation, during which all subjects maintained their original medication regimen. After the 2 weeks intervention (T1), within 24 to 48 hours following the final session, all subjects underwent the same clinical and CF assessments as the baseline assessments to identify the differences in effectiveness between the two groups and analyze the potential predictive role of baseline lipid metabolism levels on cognitive improvement.

Statistical analysis

SPSS 25.0 (IBM, Armonk, New York, USA) was employed for data analysis with a significance threshold set at $\alpha = 0.05$. The baseline data between the two groups were compared utilizing independent sample t-tests and chi-square tests. Pearson or Spearman correlation analyses were employed to explore the relationships between blood lipid markers and CF scores at the baseline stage. The core efficacy analysis used repeated measures covariance analysis with baseline cognitive scores as covariates to test the "group x time" interaction effect of intervention measures on cognitive scores. A hierarchical multiple linear regression analysis was performed to determine the predictive value of lipid metabolism. Model 1 included demographic and clinical covariates to control confounding factors, while model 2 incorporated the specific baseline lipid level (HDL-C or TG) to assess its independent and incremental predictive validity for cognitive improvement.

Results and discussion

Table 1. Correlation analysis between baseline blood lipid levels and scores in various cognitive domains.

Cognitive domain (MCCB T-score)	TC	TG	HDL-C	LDL-C
Speed of processing	-0.183	-0.214	0.198	-0.176
Attention/vigilance	-0.109	-0.168	0.211	-0.123
Working memory	-0.196	-0.248*	0.187	-0.189
Verbal learning	0.082	-0.141	0.283*	0.064
Visual learning	0.047	-0.112	0.236	0.038
Reasoning and problem solving	-0.201	-0.229	0.179	-0.198
Social cognition	-0.094	-0.153	0.162	-0.107

Note: *: $P < 0.05$.

Comparative analysis of baseline data from the two groups

The results of baseline assessment demonstrated that there were no significant differences between the groups in demographic and clinical assessments. The clinical characteristics showed that there were 128.42 ± 61.27 months and 135.18 ± 58.91 months of illness durations, while chlorpromazine equivalent dosages were 412.77 ± 153.46 and 398.54 ± 161.82 mg/day, and total PANSS scores were 78.37 ± 11.38 and 79.34 ± 10.89 in active tES stimulation and sham stimulation groups, respectively. The baseline CF and lipid profiles revealed no statistically significant differences between the two groups. Across the seven MCCB domains, the T-scores of processing speed, attention, and working memory were comparable, generally ranging between 38 and 42, which indicated a uniform level of mild-to-moderate cognitive impairment across the cohort. Similarly, lipid metabolic indicators showed high consistency with total cholesterol levels of 5.38 ± 1.02 and 5.24 ± 0.98 mmol/L in active and sham groups, respectively. There were no significant differences observed in triglycerides, HDL-C, and LDL-C levels, which confirmed that key biological and cognitive characteristics were well-balanced prior to the intervention.

Correlation between baseline blood lipid levels and CF

To explore the potential link between lipid metabolism abnormalities and cognitive impairment in patients with SZ, a correlation analysis was conducted on baseline data of all 80 participants before intervention using Pearson correlation analysis to assess the connection between four core lipid indicators and the T-scores in seven cognitive domains evaluated by MCCB. The results showed that HDL-C levels demonstrated a significant positive correlation with speech learning ability ($r = 0.283$, $P < 0.05$), indicating that patients with higher HDL-C levels also had relatively better speech learning and memory performance. The results consisted of the findings of Jenkins *et al*., which reflected the potential neuroprotective effects of cholesterol [17]. However, triglyceride (TG) levels were significantly negatively correlated with working memory ability ($r = -0.248$, $P < 0.05$), indicating that patients with higher TG levels had poorer working memory ability, which might be due to inflammation and cerebrovascular risks associated with hypertriglyceridemia [18]. In addition, the association between other blood lipid indicators and cognitive domains did not demonstrate a statistically significant level, but the overall trend suggested that poor blood lipid patterns might be related to decreased cognitive performance (Table 1).

The therapeutic effect of tES intervention on CF

To intuitively and quantitatively evaluate the intervention effect of tES on CF in patients with SZ, the research compared the cognitive domain T scores of MCCB between two groups of subjects before (T0) and after (T1) intervention. The results showed that, in terms of working memory, repeated measures covariance analysis

demonstrated a significant correlation between group and time (F (1, 77) = 8.162, *P* = 0.005, η^2p = 0.096). The working memory T-score of the active tES group significantly increased from baseline 39.56 ± 9.54 to 46.21 ± 9.88 after intervention, while no significant difference was observed in the score of the sham group. Similarly, significant group time interaction effects were observed in language learning. The T-score of speech learning in the active tES group improved from baseline 41.22 ± 10.87 to 45.38 ± 11.12 after intervention, while the improvement in the sham group ranged from 40.19 ± 11.03 to 41.07 ± 10.98. In other cognitive domains of attention/alertness, visual perception for learning, logical reasoning and problem resolution, as well as social understanding, there was no statistically significant difference between the two groups (Figure 1).

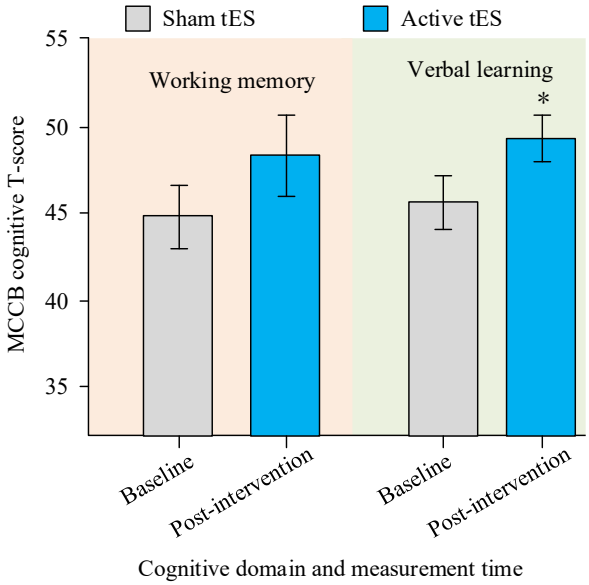

Figure 1. Intervention effect of tES on working memory and speech learning function in patients with SZ. *: *P* < 0.05 between group and time.

The cognitive improvement of the two groups in working memory and language learning showed that, in the fields of working memory and speech learning, the median T-score change of the sham tES group was close to 0, indicating that there was no substantial improvement in the cognitive performance of this group. However, the median improvement of the active tES group was significantly positive, and its interquartile range was generally above the zero mark (Figure 2). The results confirmed that anodic tES targeting the L-DLPFC could effectively improve working memory and verbal learning, which consisted with previous reports [19].

The regulatory effect of baseline blood lipid levels on the efficacy of tES

To analyze the predictors of cognitive efficacy, a hierarchical regression analysis was performed using the improvement in speech learning or working memory as the dependent variable that was the change score for verbal learning or working memory by subtracting T0 score from T1 score. The results demonstrated that, after controlling for other variables, baseline HDL-C levels could still independently explain 14.3% of the variation in speech learning improvement (ΔR^2 = 0.143, *P* = 0.014) with a positive standardized regression coefficient (β) of 0.412, indicating that patients with higher HDL-C levels had greater improvement in speech learning ability after receiving real tES treatment (Table 2). In addition, the baseline TG level could independently explain 12.1% of the variation in working memory improvement in the model (ΔR^2 = 0.121, *P* = 0.026), and its standardized regression coefficient was negative (β = -0.379), which indicated that patients with higher baseline TG levels had less significant improvement in working memory function after tES intervention (Table 3). These findings suggested that the baseline lipid metabolism status of patients might be an important biological marker for regulating the cognitive efficacy of tES with two potential mechanisms including the neuroplasticity hypothesis that suggested a healthy lipid profile providing a stable biological substrate for neuronal membrane function and the neuroinflammatory hypothesis that implied dyslipidemia-induced inflammation antagonizing the anti-inflammatory and pro-plasticity effects of tES, thereby attenuating therapeutic efficacy [20].

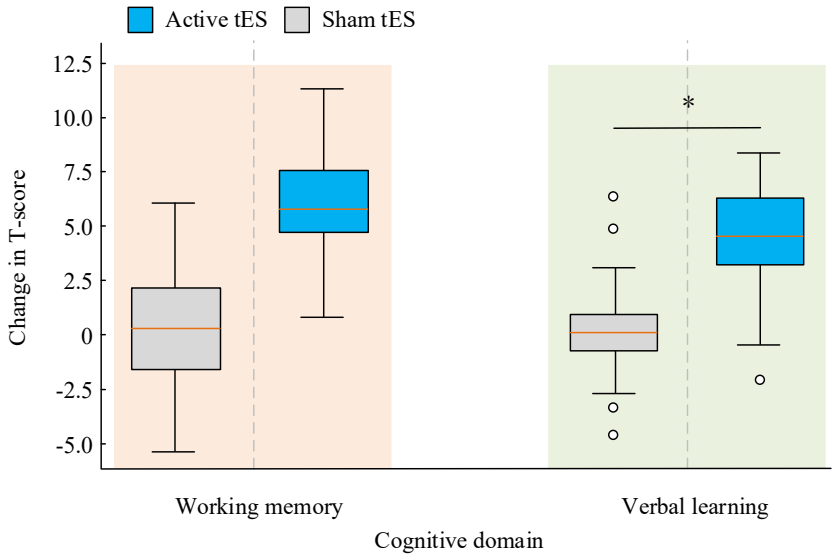

Figure 2. The cognitive improvement in working memory and speech learning between two groups. *: $P < 0.05$ between two groups).

Table 2. The predictive effect of baseline HDL-C on speech learning improvement using stratified multiple linear regression analysis.

Model	Predictor	B	SE B	β	t	*P* value	R^2	ΔR^2
1	(Constant)	6.812	3.147	-	2.164	0.037	0.086	-
	Age	-0.041	0.053	-0.134	-0.773	0.444	-	-
	Education (years)	0.188	0.169	0.189	1.112	0.273	-	-
	Duration of illness	-0.003	0.007	-0.078	-0.428	0.671	-	-
	Baseline PANSS total	-0.029	0.038	-0.131	-0.761	0.451	-	-
2	(Constant)	2.138	3.481	-	0.614	0.543	0.229	0.143*
	Age	-0.027	0.051	-0.088	-0.529	0.599	-	-
	Education (years)	0.114	0.166	0.115	0.687	0.496	-	-
	Duration of illness	-0.001	0.007	-0.026	-0.143	0.887	-	-
	Baseline PANSS total	-0.016	0.037	-0.072	-0.432	0.668	-	-
	Baseline HDL-C	7.361	2.783	0.412	2.644	0.012	-	-

Table 3. The predictive effect of baseline TG on working memory improvement using stratified multiple linear regression analysis.

Model	Predictor	B	SE B	β	t	*P* value	R^2	ΔR^2
1	(Constant)	8.024	3.518	-	2.281	0.028	0.073	-
	Age	-0.053	0.059	-0.156	-0.898	0.375	-	-
	Education (years)	0.203	0.189	0.182	1.074	0.290	-	-
	Duration of illness	-0.005	0.008	-0.109	-0.603	0.550	-	-
	Baseline PANSS total	-0.038	0.042	-0.157	-0.905	0.371	-	-
2	(Constant)	10.981	3.672	-	2.991	0.005	0.194	0.121*
	Age	-0.042	0.057	-0.123	-0.737	0.466	-	-
	Education (years)	0.237	0.184	0.212	1.288	0.205	-	-
	Duration of illness	-0.003	0.008	-0.066	-0.371	0.713	-	-
	Baseline PANSS total	-0.024	0.041	-0.099	-0.586	0.561	-	-
	Baseline TG	-2.816	1.198	-0.379	-2.351	0.024	-	-

Correlation between cognitive improvement and clinical symptom improvement

To investigate whether the CF improvement brought by tES intervention was related to the improvement of other clinical dimensions, the study further analyzed the relationship between cognitive improvement and mental symptom improvement within the active tES group by calculating the T-score changes of each participant in the fields of working memory and speech learning, as well as their score changes on the PANSS subscales including positive, negative, general psychopathology, and total score. Pearson correlation analysis results showed that there was a significant inverse correlation between the improvement in working memory and the reduction in negative symptoms. Additionally, the improvement in verbal learning was negatively associated with the reduction in PANSS total scores. These results indicated that patients who exhibited greater cognitive gains, particularly in working memory, experienced more substantial alleviation of negative symptoms such as emotional apathy and avolition.

Conclusion

The results of this study suggested that blood lipid levels could serve as accessible biomarkers for predicting tES therapeutic response. Therefore, integrating metabolic interventions with tES might represent a viable strategy and could optimize treatment outcomes for SZ. However, this study was limited by sample size and intervention duration. Future research should validate these results in larger cohorts and utilize neuroimaging techniques to unravel the underlying brain network mechanisms.

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