ORIGINAL RESEARCH

Imaging Study of Electroconvulsive Modulation of Brain Markers of Emotional Processing and Activation of Various Brain Regions in Schizophrenic Patients

Jianying Xiao, MD; Juan Wang, PhD; Dongxin Wang, PhD

ABSTRACT

Aims • An imaging study to investigate electroconvulsive modulation of brain markers of emotional processing and activity of various brain regions in patients with schizophrenia.

Materials and methods • One hundred and twenty patients with schizophrenia admitted to The Brain Hospital of Hunan Province from January 2020 to July 2022 were divided into a comparison group and a study group of 60 patients each according to the order of admission. The comparison group received conventional pharmacological interventions and the study group implemented conventional pharmacological and electroconvulsive modulation therapy to compare the neurotransmitter power, neuropsychological assessment, and efficacy evaluation between the two groups.

Results • Before treatment, there was no statistically significant difference in neurotransmitter power between the two groups ($P > .05$); 30 min after treatment, GABA, Glu, 5-HT, Ach, NE, and DA were elevated in both groups and were higher in the study group than in the comparison group, and the difference was statistically significant ($P < .05$). Before treatment, there was no statistically significant difference in the neuropsychological measurements between the two groups ($P > .05$). Clinical efficacy evaluation after treatment revealed that the clinical efficacy rate of patients in the study group was 95.00% significantly higher than that of the comparison group, which was 83.33%, and the comparative difference was statistically significant ($P < .05$).

Conclusion • Electroconvulsive therapy was found to significantly improve neuropsychological assessment and clinical outcomes in patients with psychiatric disorders. (*Altern Ther Health Med.* [E-pub ahead of print.])

Jianying Xiao, MD; Department of Psychiatry, The Hunan Brain Hospital (The Second People's Hospital of Hunan Province), Changsha, Hunan, China; **Juan Wang, PhD;** Department of Radiology, The Hunan Brain Hospital (The Second People's Hospital of Hunan Province), Changsha, Hunan, China; **Dongxin Wang, PhD;** Department of Mental Health Institute, The Hunan Brain Hospital (The Second People's Hospital of Hunan Province), Changsha, Hunan, China.

Corresponding author: Dongxin Wang, PhD
E-mail: 330247@hnucm.edu.cn

INTRODUCTION

Schizophrenia is one of the most common severe psychiatric disorders in psychiatry, often with specific disorders of various aspects of thinking, perception, emotion, and behavior and a mountain of incompatibility between mental activity and the environment, without the ability to recognize the condition during its onset.[1] The lifetime prevalence in the population is about 1%, and the recurrence rate is high, with about 10% of patients experiencing suicide and the possibility of chronicity and decline of the disease.[2] Schizophrenia is treated with various measures, including medication, psychotherapy, and physiotherapy.[3] Among physical treatments, electroconvulsive therapy is the most common, electroconvulsive therapy is a treatment that stimulates the brain with a brief moderate amount of electric current to cause loss of consciousness, widespread cortical EEG emission, and generalized convulsions in patients to achieve control of psychiatric symptoms.[4] With the efficacy of the technique, intravenous anesthetics and muscle relaxants are now mostly used preoperatively to reduce convulsions and patient fear, which is also known as electroconvulsive therapy because it is widely accepted for its higher safety and fewer complications than traditional electroconvulsive therapy.[5] Electroconvulsive shock is now widely available and used worldwide, and although it has been used in clinical practice for decades, there is still a lack of clarity regarding the neurological mechanisms of electroconvulsive therapy.[6]

Studies have shown that emotional dysfunction is the main cause of social dysfunction in patients with schizophrenia, who have difficulty expressing emotions appropriately, have reduced expectations of happy events, have difficulty

recognizing and facing emotions, and are more likely to experience negative emotions. With the development of brain imaging technology in recent years, brain imaging studies on emotional dysfunction in schizophrenia patients have emerged.[7,8] It was found that amygdala-related neural networks have a complex role in emotional processing impairment in schizophrenia and that reduced activation between the amygdala and several brain regions, especially with the anterior cingulate gyrus and dorsolateral prefrontal lobe of the person, leads to difficulties in integrating emotion and cognition in schizophrenia patients.[9] It was found that electroconvulsive therapy significantly improved dynamic facial expressions in patients with psychiatric disorders, and our previous clinical trial found that electroconvulsive therapy improved psychotic symptoms in patients with schizophrenia.[10] We hypothesise that electroconvulsive therapy significantly improves neuropsychological assessment and clinical outcomes in patients with psychiatric disorders.

We, therefore, conducted this study to explore electroconvulsive modulation of brain markers of emotional processing and activity of various brain regions in patients with schizophrenia. Our study suggests that abnormalities in network connectivity and metabolism of the amygdala and related brain regions can cause difficulties in integrating emotional processing in patients with schizophrenia. Electroconvulsive therapy may improve emotional processing disorders in schizophrenia patients by improving network connectivity and metabolism between the amygdala and related brain regions.

MATERIAL AND METHODS

Research object

This study is retrospective. This includes the cause and symptoms of schizophrenia, the duration of the disease, previous treatment, medications taken, and family history. The presence of other organic diseases, history of surgery, and history of trauma were recorded, and a detailed physical examination was performed. The 120 patients with schizophrenia admitted to our hospital from January 2020 to July 2022 were divided into a comparison group and a study group of 60 patients each according to the order of admission. Schizophrenia diagnostic criteria with the American Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition[11], were confirmed by two psychiatrists with clinical experience at the level of deputy chief physician or above through consistency testing. This study was approved by the Ethics Committee of the Brain Hospital of Hunan Province.

Inclusion and exclusion criteria

For patients to be included in the study, they must meet the following criteria: 1. Have a Positive and Negative Syndrome Scale (PANSS) total score of at least 60 points, have completed a full course of antipsychotic drug treatment without improvement, meet the indications for electroconvulsive shock, have no contraindications, and have not received any treatment within the past 6 months. 2. Meet the diagnostic criteria for schizophrenia according to DSM-V. 3. Have laboratory values within normal range for electrocardiogram, blood test, and biochemical test including liver, kidney, blood sugar, and thyroid function. They must also fully understand the study and willingly participate by signing the informed consent form with the legal guardian's approval. For healthy controls to be included, they must be healthy, right-handed, and aged between 18 and 50 years old. The controls should be matched according to their age and educational level.

The following are the exclusion criteria for this study: 1. Individuals with a history of neurological or major physical diseases, as well as those with a history of alcohol or drug abuse or dependence. 2. Individuals who are at risk of seizures, including those with abnormal EEG, a history of trauma or idiopathic epilepsy, and those who use neurostimulant drugs. Pregnant and lactating women are also excluded. 3. Those without follow-up data after inclusion, those who have participated in the schizophrenia clinical trial more than once, and those who meet the inclusion criteria but were not randomly assigned by the investigator by regulations are also excluded.

Additionally, those who have already received a course of treatment or who do not accept the treatment prescribed by the regulations are excluded. Individuals who cannot receive further treatment due to changes in their condition during the treatment process are also excluded. Lastly, individuals whose evaluation of therapeutic efficacy was affected by the use of other treatment methods or experienced adverse reactions during the treatment process are also excluded.

Methods

The comparison group received conventional pharmacological interventions, according to the "Chinese Guidelines for the Prevention and Treatment of Schizophrenia" published by the Psychiatry Branch of the Chinese Medical Association in 2015.[12] In this study, the currently clinically recognized schizophrenia-positive drug Risperidone tablets were used. The dose was fixed at 3-6 mg orally 0.5 h after breakfast daily for 3 weeks. In the study group, electroconvulsive therapy was administered based on control, i.e. electrocardiogram, chest X-ray, blood routine, and blood biochemistry were checked before treatment, weight was measured, routine water and food fasting for 6h, and intravenous compound general anesthesia was used. The patient was treated with the Thymatorn TM DGx IV non-convulsive electroconvulsive therapy device (manufacturer: American Eagle Medical Technology), and the electrodes were placed on both hazel sides of the treatment area, with standard pulse stimulation, and the energy percentage was set according to 2/3 of the patient's age. The course of MECT was 8-12 times, 3 times a week, for 3 weeks (depending on the later stage of treatment). The antipsychotic regimen remained unchanged, including the type, amount, and timing of administration.

MRS examination method: In the paramedian sagittal section, an oblique coronal LAR sequence T1WI scan (T1-FLAIR) was performed perpendicular to the long axis of

the right hippocampus. The *N*-acetyl aspartate/creatine (NAA/Cr) and choline/creatine (Cho/Cr) ratios in the amygdala 1H-MRS were characterized. MRI methods: 1. Scanning procedure and data processing: whole-brain structural images were acquired using fast perturbed phase gradient echo (3D-FSPGR) and Bold sequences. All data were processed under functional brain image analysis software (AFI), statistical parametric mapping software SPM8, and Matlab version 7.0 package. 2. Define the seed region: the amygdala was selected as the seed region, and the boundary of the bilateral amygdala was determined. The size and volume of the amygdala on the functional image were obtained. 3. Amygdala Functional Connectivity (AFC): After completing the above steps, the time course of bilateral amygdala was extracted by AFNI software and averaged as the seed area (3 dmaskave), and then the time course of the seed area was correlated with the whole brain based on Pearson correlation method (3 dmaskave). The correlation coefficients of each pixel obtained were transformed by Fisher to produce values close to the normally distributed correlation coefficient variable m. Then, the anatomical image of itself was transformed into Talairach standard space and selected as a template to transform the resolution of the data obtained from the functional image into $2\times2\times2m^3$ standard space (adware), and subsequently, the AFC functional Amygdala Functional Connectivity map of each subject was obtained by 6-mm FWHM Gaussian kernel smoothing. The obtained whole-brain pixel-based correlation coefficient maps of the subjects were subjected to one-sample *t*-tests to generate several groups of AFC functional connectivity neural network maps separately, to obtain the neural network patterns of the subjects' brain AFC functional connectivity. To compare the differences in AFC neural network patterns, 30 brain regions related to emotional processing were selected as regions of interest, including the bilateral medial frontal cortex, OFC, dorsolateral prefrontal cortex, frontal medial cortex, inferior frontal cortex, middle hazel cortex, posterior cingulate gyrus, inferior parietal lobule, precuneus, insula, hippocampus, thalamus, caudate nucleus, and shell nucleus. Each ROI was multiplied by the published coordinates of a sphere of 4 mm radius as a mask, and multiplied by the AFC neural network pattern map of each subject, and the CC value of each ROI was extracted, while its mean was used as the standard, and a two-sample t-test was performed based on each ROI, to find differences between the two groups in the AFC neural network loops.

Observation indicator

Neuropsychological assessment: All subjects were investigated using the self-administered general condition scale, the social pleasure deficit scale (RSAS-C), the Chinese version of the Revised Somatic Pleasure Deficit Scale (RPAS-C), and the Chinese version of the Interpersonal Response Indicator Inventory (IRI-C), the Positive and Negative Symptom Scale (PANSS), and the clinical outcome. 1.RSAS-C:[13] A total of 40 items were used to assess the extent to which subjects experience pleasure in social aspects. A score of 1 was given for a "yes" or "no" response, and a score of 0 was given for an answer consistent with the standard answer. The higher the score, the lower the degree of experiencing pleasure in social interpersonal interactions, i.e., the more serious the social pleasure deficit. 2. RPAS-C:[14] A total of 61 items were used to assess the degree of somatic pleasure experienced by the subjects. A score of 1 was given for a "yes" or "no" response, and a score of 0 was given for an agreement with the standard answer. The higher the score, the lower the degree of experiencing somatic pleasure, that is, the more serious the lack of somatic pleasure. 3.IRI-C:[15] It consists of 22 items, including four factors, namely, perspective taking, imagination, empathic concern, and personal distress, and is scored on a scale of 0 to 4, with higher scores indicating higher empathic ability. 4.PANSS:[16] The assessment index includes total score, positive symptom score, and negative symptom score, and the higher score indicates the more severe the corresponding psychiatric symptoms of the patient. Efficacy determination criteria: the reduction rate was assessed by the PANSS scale, ≥75% was considered clinically cured, 50%-74% was considered significantly efficacious, 25%-49% was considered efficacious, and <25% was considered ineffective.

Statistical analysis

The sample size for this study was calculated according to the prevalence of the disease. It was computed using the following formula: $n=Z^2(p\times q)/d^2$. Z=1.96; p=0.8; q=1-p; and d is a fraction of p. All data from our study were checked using Excel double entry, and SPSS version 23.0 software was used for data analysis. The measurement data was described by mean ± standard deviation and compared by using a *t* test, and count data were described by frequency and composition ratio and compared by using the chi-square test. The difference was statistically significant when $P < .05$.

RESULTS

General data comparison

Before treatment, there was no significant difference in neurotransmitter power between the two groups ($P > .05$); 30 minutes after treatment, the levels of GABA, Glu, 5-HT, Ach, NE, and DA in the two groups were increased, and those in the study group were higher than those in the control group ($P < .05$) (Figure 1).

Comparison of neuropsychological measurements between the two groups

Before treatment, there was no significant difference in neuropsychological measurements between the two groups ($P > .05$); after treatment, the IRI-C score of the study group

Table 1. Comparison of general data of the two groups of patients

Group	Gender (male/female)	Age (years)	Duration of illness (months)	Duration of education (years)
Comparison group (n = 60)	37/23	23.90±3.71	12.35±2.19	12.19±3.77
Research groups (n = 60)	39/21	23.10±3.62	12.32±2.17	12.36±3.52
t/χ^2	0.144	1.195	0.075	-0.255
P value	.705	.234	.94	.799

Figure 1. Comparison of neurotransmitter power. (A) GABA. (B) Glu. (C) 5-HT. (D) Ach. (E) NE. (F) DA.

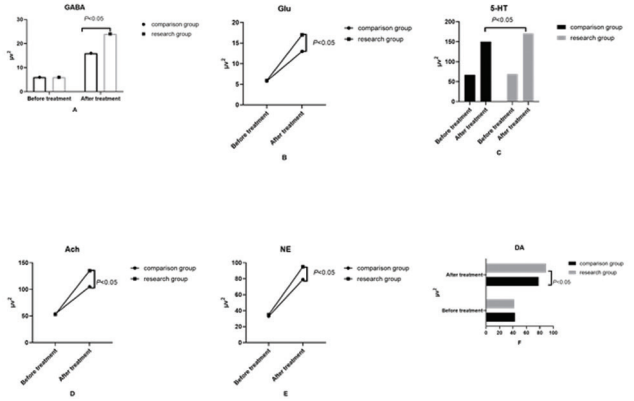


Figure 2. Comparison of neuropsychological measurement values between the two groups. (A) RSAS-C. (B) RPAS-C. (C) IRI-C. (D) PANSS.

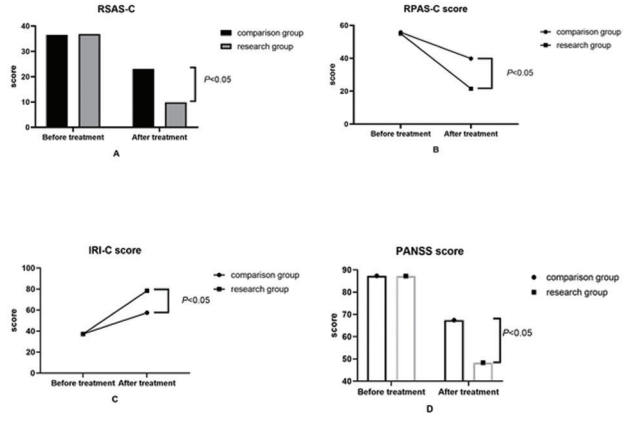
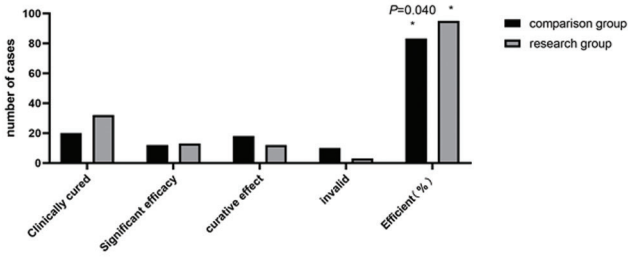


Figure 3. Clinical efficacy evaluation.



was higher than that of the control group, but the RSAS-C score, RPAS-C score, and PANSS score of the study group were significantly lower than the control group ($P < .05$) (Figure 2).

Clinical efficacy evaluation

The clinical efficacy evaluation after treatment showed that the clinical efficacy rate of patients in the study group was 95.00%, which was significantly higher than that in the control group, which was 83.33% ($P < .05$) (Figure 3).

DISCUSSION

Schizophrenia is a type of chronic migratory disease in which patients have cognitive and social deficits and are difficult to maintain normal life and interpersonal interactions, and rely on antipsychotics to suppress symptoms.[17] Electroconvulsive therapy has been used in the treatment of mental disorders for more than 70 years. Although its efficacy and safety have been confirmed in randomized controlled trials, the specific mechanism of action is still unclear.[18] Electroconvulsive therapy has a rapid and precise curative effect on mental diseases, but the mechanism of action is still unclear. Elucidating this mechanism will not only help us understand the etiology of mental diseases but also may expand new treatment methods based on this.[19] The development of imaging technology in recent years has provided an opportunity and hope for further clarifying the onset mechanism of electroconvulsive therapy.

Our study found that after treatment, the IRI-C score of the study group was higher than that of the control group, but the RSAS-C score, RPAS-C score, and PANSS score of the study group were significantly lower than those of the control group, indicating that electroconvulsive therapy can significantly improve the neurological conditions of patients with mental disorders. Psychological assessment: Patients with schizophrenia have different degrees of impairment of emotional cognition and processing, mainly manifested as emotional perception, emotional experience, and interaction between emotion and cognition. Emotional perception disorder mainly refers to the difficulty in recognizing facial emotions.[20]

Our study found that the GABA, Glu, 5-HT, Ach, NE, and DA of the two groups of patients all increased 30 minutes after treatment, and the research group was higher than the control group. 5-HTiA receptor binding is generally downregulated after electroconvulsive therapy in schizophrenia patients. Some scholars found that PET was used as a research tool, and the highly selective carboxyl (11C) radioligand WAY100635 was selected as a tracer to measure the changes of 5-HTA receptor binding in the brains of 12 patients with severe refractory schizophrenia before and after electroconvulsive therapy.[21] The study found that 5-HT1 receptor binding was down-regulated in a wide range of brain regions in schizophrenia patients after electroconvulsive therapy, especially in the anterior cingulate gyrus, orbitofrontal cortex, amygdala, hippocampus, and insula. Postsynaptic 5-HT14 receptors are believed to be involved in the mechanism of action of electroconvulsive therapy.[22,23] The same study found that 15 patients with refractory schizophrenia underwent drug-eluting in the baseline period before electroconvulsive therapy treatment, using (18F) stopperone as a tracer, and found that 5-HT2 receptors were common in the brain of schizophrenia patients after electroconvulsive therapy. Down-regulation, more prominent in the right hemisphere, and down-regulation of 5-HT2 receptors in the right parahippocampal gyrus, right lingual gyrus, and right medial frontal cortex was associated with the improvement of schizophrenia, indicating that the down-regulation of 5-HT2 receptors may be the antipsychotic mechanism of fission.[24] Studies have shown that

Flinders Sensitive Line (FSL) rats with poor adaptability and high cholinergic sensitivity have the behavioral characteristics of schizophrenia and can be used as a genetic animal model for schizophrenia.[25] Studies have found that ECS can down-regulate α2-adrenergic receptors in the cortex and amygdala of FSL rats, and it is believed that the therapeutic effect of ECS may be mediated by reducing α2-adrenergic receptors and continuously increasing the release of norepinephrine.[26] Electroconvulsive therapy may ameliorate schizophrenia emotional processing disorder by modulating the metabolism of amygdala-related neural network connections.[27] Convulsive electroconvulsive therapy (MECT) is a safe and effective method for the treatment of schizophrenia, but its therapeutic mechanism is not fully understood.

Based on previous research on schizophrenia, we explored the emotional processing disorder of schizophrenia patients based on the amygdala-related neural network. We not only paid attention to the influence of the amygdala-related neural network on the emotional processing of schizophrenia patients but also based on our previous clinical experiments. Found the therapeutic effect of electroshock on schizophrenia, using electroshock as an intervention to explore whether electroshock can improve emotional processing disorders through the amygdala-related neural network.[28] Not only pays attention to the application of neuropsychological assessment but also introduces the research paradigm of radionics into the research field of schizophrenia emotional processing disorder, making the research method more scientific and rich change.

Our study has some limitations: First, to objectively evaluate the effect of electroconvulsive therapy, we included patients with inadequate drug treatment in a sufficient amount and a full course of treatment. However, due to ethical factors, the use of antipsychotic drugs was not controlled during electroconvulsive therapy. A possible effect of the drug cannot be completely ruled out. Due to the limitations of time, human resources, funding, and other conditions, no follow-up studies have been conducted on schizophrenia patients treated with drugs alone. Similarly, patients will use narcotic drugs during electroshock, but MRI scans after electrification can rule out their effects on brain function. Studies have shown that the use of antipsychotic drugs may lead to increased low-frequency amplitudes and weakened functional connectivity, propofol may lead to weakened functional connectivity between brain regions, and anesthetic drugs may not lead to improvement of patients' psychiatric symptoms. However, in this study, the low-frequency amplitude was decreased and the functional connectivity was enhanced after electroshock. Based on this, it is speculated that the use of antipsychotics and anesthetics did not have a significant impact on the findings of this study. Therefore, future research can conduct MRI scans at more time points during electroconvulsive therapy, further expand the sample size, and conduct comparative analysis with drug therapy, to obtain electroconvulsive specific and stable imaging markers, which is conducive to deepening the Understanding of brain imaging mechanisms of electroconvulsive antipsychotic effects.

In conclusion, the study found that electroconvulsive therapy can significantly improve the neuropsychological assessment of patients with mental disorders and improve clinical efficacy. However, this conclusion remains to be confirmed by further expanding the scope of sample selection in the future.

FUNDING

This study was supported by the Natural Science Foundation of Hunan Province (no. 2020JJ8009).

REFERENCES

1. Yu M, Tan Q, Wang Y, et al. Correlation between duration of untreated psychosis and long-term prognosis in chronic schizophrenia. *Front Psychiatry*. 2023;14:1112657. doi:10.3389/fpsyt.2023.1112657
2. Wiszniewski B, Liberska H. Styles of Coping with Stress among Healthy People and People with Diagnosis of Schizophrenia and Selected Personality Dimensions. *Int J Environ Res Public Health*. 2022;19(9):5129. doi:10.3390/ijerph19095129
3. Chan V. Schizophrenia and Psychosis: Diagnosis, Current Research Trends, and Model Treatment Approaches with Implications for Transitional Age Youth. *Child Adolesc Psychiatr Clin N Am*. 2017;26(2):341-366. doi:10.1016/j.chc.2016.12.014
4. Batinic B. Cognitive Models of Positive and Negative Symptoms of Schizophrenia and Implications for Treatment. *Psychiatr Danub*. 2019;31(suppl 2):181-184. https://pubmed.ncbi.nlm.nih.gov/31158119/
5. Richetto J, Meyer U. Epigenetic Modifications in Schizophrenia and Related Disorders: Molecular Scars of Environmental Exposures and Source of Phenotypic Variability. *Biol Psychiatry*. 2021;89(3):215-226. doi:10.1016/j.biopsych.2020.03.008
6. Zamanpoor M. Schizophrenia in a genomic era: a review from the pathogenesis, genetic and environmental etiology to diagnosis and treatment insights. *Psychiatr Genet*. 2020;30(1):1-9. doi:10.1097/YPG.0000000000000245
7. Li M, Jiang Z, Wen R, Liu C, Wang J. A bibliometric analysis of the application of imaging in sleep in neurodegenerative disease. *Front Aging Neurosci*. 2023;15:1078807. doi:10.3389/fnagi.2023.1078807
8. Iliuta FP, Manea MC, Budisteanu M, Ciobanu AM, Manea M. Magnetic resonance imaging in schizophrenia: luxury or necessity? (Review). [Review]. *Exp Ther Med*. 2021;22(1):765. doi:10.3892/etm.2021.10197
9. Alkozei A, Dailey NS, Bajaj S, Vanuk JR, Raikes AC, Killgore WDS. Exposure to Blue Wavelength Light Is Associated With Increases in Bidirectional Amygdala-DLPFC Connectivity at Rest. *Front Neurol*. 2021;12:625443. doi:10.3389/fneur.2021.625443
10. Bracht T, Walther S, Breit S, et al. Distinct and shared patterns of brain plasticity during electroconvulsive therapy and treatment as usual in depression: an observational multimodal MRI-study. *Transl Psychiatry*. 2023;13(1):6. doi:10.1038/s41398-022-02304-2
11. Shabsigh R, Rowland D. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision as an Appropriate Diagnostic for Premature Ejaculation. *The Journal of Sexual Medicine*. 2007;4(5):1468-1478. doi:10.1111/j.1743-6109.2007.00557.x
12. Si TM, Wu RR. Chinese Guidelines for the Prevention and Treatment of Schizophrenia. *China Journal of Psychiatry*. 2023;56(5):331-335. doi:10.3760/cma.j.cn113661-20230520-00104
13. Pardiñas AF, Holmans P, Pocklington AJ, et al; GERAD1 Consortium; CRESTAR Consortium. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat Genet*. 2018;50(3):381-389. doi:10.1038/s41588-018-0059-2
14. Abel KM, Elliott RE, Downey D, et al. Preliminary evidence for neural responsiveness to infants in mothers with schizophrenia and the implications for healthy parenting. *Schizophr Res*. 2018;197:451-457. doi:10.1016/j.schres.2017.11.033
15. Solberg BS, Halmøy A, Engeland A, Igland J, Haavik J, Klungsøyr K. Gender differences in psychiatric comorbidity: a population-based study of 40 000 adults with attention deficit hyperactivity disorder. *Acta Psychiatr Scand*. 2018;137(3):176-186. doi:10.1111/acps.12845
16. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261-276. doi:10.1093/schbul/13.2.261
17. Kane JM, Agid O, Baldwin ML, et al. Clinical Guidance on the Identification and Management of Treatment-Resistant Schizophrenia. *J Clin Psychiatry*. 2019;80(2):18com12123. doi:10.4088/JCP.18com12123
18. Marques TR, Ashok AH, Pillinger T, et al. Neuroinflammation in schizophrenia: meta-analysis of *in vivo* microglial imaging studies. *Psychol Med*. 2019;49(13):2186-2196. doi:10.1017/S0033291718003057
19. Driver DI, Thomas S, Gogtay N, Rapoport JL. Childhood-Onset Schizophrenia and Early-onset Schizophrenia Spectrum Disorders: an Update. *Child Adolesc Psychiatr Clin N Am*. 2020;29(1):71-90. doi:10.1016/j.chc.2019.08.017
20. Krynicki CR, Upthegrove R, Deakin JFW, Barnes TRE. The relationship between negative symptoms and depression in schizophrenia: a systematic review. *Acta Psychiatr Scand*. 2018;137(5):380-390. doi:10.1111/acps.12873
21. Javed A, Charles A. The Importance of Social Cognition in Improving Functional Outcomes in Schizophrenia. *Front Psychiatry*. 2018;9:157. doi:10.3389/fpsyt.2018.00157
22. Khitha V, Tayade S. Application of Deep Brain Stimulation in Refractory Post-Traumatic Stress Disorder. *Cureus*. 2023;15(1):e33780. doi:10.7759/cureus.33780
23. Wang L, Wang M, Zhao C, Jian J, Qiao D. Association of HTR3B gene polymorphisms with depression and its executive dysfunction: a case-control study. *BMC Psychiatry*. 2023;23(1):128. doi:10.1186/s12888-023-04625-y
24. Mote J, Kring AM. Facial emotion perception in schizophrenia: does sex matter? *World J Psychiatry*. 2016;6(2):257-268. doi:10.5498/wjp.v6.i2.257
25. Maher S, Ekstrom T, Chen Y. Impaired visual cortical processing of affective facial information in schizophrenia. *Clin Psychol Sci*. 2016;4(4):651-660. doi:10.1177/2167702615609595
26. Kim JH, Youn T, Choi JG, et al. Combination of Electroconvulsive Therapy and Clozapine in Treatment-Resistant Schizophrenia. *Psychiatry Investig*. 2018;15(8):829-835. doi:10.30773/pi.2018.05.15
27. Dedic N, Kühne C, Jakovcevski M, et al. Chronic CRH depletion from GABAergic, long-range projection neurons in the extended amygdala reduces dopamine release and increases anxiety. *Nat Neurosci*. 2018;21(6):803-807. doi:10.1038/s41593-018-0151-z
28. Jacob S, Landolfo KP, El-Sayed Ahmed MM, Thomas M, Makey IA, Pham SM. Electric shock-induced cardiac injuries requiring surgical intervention: case series and a brief review. *J Card Surg*. 2020;35(2):488-491. doi:10.1111/jocs.14382