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The overview of promising nonpharmacological treatments to improve the cognitive performance of schizophrenia patients

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Abstract. Schizophrenia is a complex neuropsychiatric disorder that could bring severe cognitive and neurological dysfunctions to patients. Current widely used treatments, such as second-generation antipsychotics, are only effective in addressing the positive symptoms of the disorder, rather than the negative symptoms and cognitive dysfunctions experienced by patients. Moreover, these medications lack personalized treatment, as they do not cater to the individual needs of each patient. Given these limitations, there is a pressing need to explore more innovative, nonpharmacological treatments that specifically target the improvement of negative and cognitive symptoms in schizophrenia patients. This paper, through literature review and case analysis, will delve into the various aspects of schizophrenia, including its symptoms, pathology, etiology, and diagnosis. Additionally, it will provide a comparative analysis of traditional and innovative treatment approaches, highlighting the potential benefits of exploring alternative, non-pharmacological interventions that may better address the multifaceted nature of this complex disorder.

Keywords: Schizophrenia, second generation-antipsychotic, nonpharmacological treatments.

1. Introduction

Schizophrenia is a chronic and heterogeneous mental disorder. This disorder has a significant impact on individuals' cognitive, emotional, and behavioral functioning within their living environment. Approximately 1 percent of the US general population is affected by schizophrenia. Tons of scholars and studies have studied schizophrenia for more than a century. However, given the complex nature of this disorder, the questions about schizophrenia are still too much for people to understand.

Tandon and other scholars have mentioned various risks associated with schizophrenia, including genetic, complication, and environmental risks [1]. For instance, individuals diagnosed with schizophrenia have a higher likelihood of developing other psychiatric disorders, such as bipolar disorder, which could also be associated with increased drug use and crime rates.

This paper discusses both traditional and innovative treatments for schizophrenia. As mentioned in the study of Miyamoto, although pharmacological treatments have been widely used and proved to be effective for the positive symptoms of schizophrenia, there are many other negative effects of these medications [2]. Therefore, nonpharmacological treatments seem to be more promising options for the patients.

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2. Symptoms of Schizophrenia

The symptoms of people with schizophrenia are basically having experiences that seem out of touch with reality, being unable to distinguish between imagination and the real world and having difficulties in their daily social lives. Since schizophrenia is a heterogeneous, very complex disorder, the symptoms can vary extensively across people. Normally, symptoms can be categorized into three types, positive symptoms, negative symptoms, and cognitive deficits. Positive symptoms usually include delusion (a false belief that people who are not there are real people), hallucination (which typically involves engaging multiple senses, such as hearing and seeing, to perceive things that are not physically present), and disorganized speech and behaviors. Some classical examples of positive symptoms of people with schizophrenia (SCZ) are persecutory delusions that people think they are tortured or spied on, referential delusions that people think some environmental cues such as newspapers and TV shows are referring to themselves, and grandeur delusion that patients think they have great talents or power just like superheroes. Moreover, patients may exhibit disorganized behavior and thinking, as well as catatonic motor behaviors. For negative symptoms, there are some typical symptoms, such as lacking normal emotions, behaviors, and motivations. Affective flattening is a typical symptom for patients, which refers to the limitation of range and intensity of emotional expression. Alogia, Avolition and Anhedonia are the other typical symptoms that respectively mean a decrease in speech production, a decrease in goal-oriented behavior, and a lack of pleasure.

In addition to experiencing positive and negative symptoms that deviate from normal thinking and behavioral patterns, individuals with schizophrenia often exhibit cognitive deficits.Those deficits usually involve a lack of working memory, attention, motor, etc., which might hinder them from living a normal social life. The ability to gate out sensory disturbances is a typical symptom that makes lots of SCZ patients suffer. Sensory disturbance means “an inability to filter out extraneous noise from meaningful sensory inputs [3].”

It is noteworthy to mention that Schizophrenia does not involve personality splits, not as some media portraits suggest.

3. Pathology and etiology

3.1. Pathophysiology

Although lots of efforts have been made to study the cause of schizophrenia, the molecular pathology remains unknown. Thankfully, there are huge progress in the knowledge of the relationship between the risk of getting schizophrenia and changes in DNA sequences [4]. Clinical research has provided evidence that prefrontal dysfunction is positively related to schizophrenia. The negative symptoms and cognitive symptoms of schizophrenia might be related to the dysfunction of working memory in the prefrontal area of the brain [5]. From the perspective of neurological mechanisms, most theories state that abnormal activities of dopamine and glutamate are the basis for the pathophysiology of SCZ. The abnormal activities of these two neurotransmitters are likely to lead to a reduction in frontal activation, which is referred to as hypofrontality. The activity of the dorsal lateral prefrontal cortex (DLPFC) is lower in SCZ patients than in control groups. There is a study showing that DLPFC is crucial to human working memory, especially when participants are manipulating verbal and spatial information [6-8].

3.2. Etiology

Researchers are still unsure of the exact cause of SCZ, but it is essentially a biological problem that involves molecular and functional changes in the brain. However, certain external factors, such as major life stress or substance use, can act as triggers. It is widely believed that it comes from genetic and environmental influences. There is scientific evidence showing that the risk of one of a pair of monozygotic twins is significantly higher than that of a dizygotic twin [9].

There is other research speculating that schizophrenia may be related to inflammation and infection, especially for those people with a higher genetic risk of getting schizophrenia from their relatives. Some serious parental or childhood infections are associated with an increased risk of getting schizophrenia in

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the future [10]. Treatment targeting inflammation in the brain has demonstrated a positive effect on the symptoms of schizophrenia, potentially bolstering the credibility of the inflammation and infection hypothesis. As Ahmed mentioned, some specific pathogens, including Toxoplasma gondii, herpesviruses, Chlamydophila, and more, may be another cause of schizophrenia [10].

3.3. Diagnosis

The symptoms of schizophrenia should be examined under strict rules based on the duration of the patients showing positive and negative symptoms, along with cognitive symptoms such as loss of working memory. For positive symptoms, clinicians should score four aspects: hallucinations, delusions, bizarre behaviors, and positive formal thought disorder; for negative symptoms, affective flattening, Alogia, Avolition-apathy, Anhedonia-asociality, and attention [11]. Clinicians need to verify that the symptoms do not stem from the use of other substances or medications.

4. Treatment Overview

4.1. Traditional Pharmacological Treatment

The current dominant treatment is the pharmacological method. The most commonly used medication is second-generation antipsychotics, with first-generation antipsychotics preceding. Although this conventional treatment has proven to be effective on the positive symptoms of schizophrenia, it does no effect on improving the negative or cognitive symptoms. Approximately 10% to 30% of individuals diagnosed with schizophrenia do not see significant improvement in symptoms after undergoing numerous trials of first-generation antipsychotics (FGAs). Additionally, an additional 30% to 60% of patients either experience only partial or inadequate improvement or encounter severe side effects during antipsychotic medication [12]. Clozapine is most effective for treatment-resistant schizophrenia patients, but it can still increase the probability of getting orthostatic hypotension [12]. Another disadvantage of these antipsychotics is the limited availability of personalized therapeutic options. Consequently, there is a growing need for more innovative and individualized treatment approaches in the future.

4.2. Nonpharmacological Treatment

4.2.1. ECT

Electroconvulsive Theory (ECT) is shown to be safe and effective for people with schizophrenia, especially when combined with pharmacological treatment. Grover and others discussed several meta-analyses, reviews, and clinical practice guidelines in their review [13]. The authors note that while most of the studies conclude that ECT has a beneficial effect in managing schizophrenia, the quality of the evidence is limited due to small sample sizes and inferior study designs. The authors also mention that the combination of ECT and antipsychotic medication may be more effective in treating refractory schizophrenia. There are still some apparent but mild side effects of ECT. Almost all patients have some side effects on their cardiovascular system, though most cases are not severe.

4.2.2. rTMS

The use of repetitive transcranial magnetic stimulation (rTMS) is a potential treatment for schizophrenia [14]. That essay also emphasizes the importance of assessing depressive and negative symptoms throughout the study, as well as the potential benefits of individualized targeting based on functional imaging. In the review of Mehta, it is mentioned that rTMS targeting the language processing regions of the left hemisphere has proven to be effective in improving the auditory-verbal hallucinations of patients [15].

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4.3. Neurological Approaches

4.3.1. Gamma entrainment using sensory stimulation (GENUS)

GENUS is a novel method aiming to entrain impaired oscillatory network activity and restore brain function that utilizes sensory stimulation, such as music listening, to address impaired gamma frequency entrainment observed in patients, particularly in response to auditory and visual stimuli. Clinical trials for GENUS demonstrated feasibility, safety, adherence, and potential therapeutic benefits in patients with prodromal Alzheimer's disease. Animal models also show promise in improving not only as a therapeutic intervention but also as a spatial and recognition memory, lowering the buildup of plaque potential diagnostic biomarkers, and improving synaptic function in various parts of the brain [16].

4.3.2. EEG Neurofeedback

The lab of Dr. Singh tried to use neurofeedback (NFB) as a neuromodulatory approach that allows individuals to modulate their brain activity. This approach shows promise for various disorders, like mild cognitive impairment. NFB involves conscious manipulation of EEG activity, enabling personalized treatment approaches and leading to structural brain changes.

Patients with schizophrenia often experience persistent negative symptoms and cognitive deficits despite pharmacological treatments. NFB treatments are not specific to particular symptoms, making this approach applicable across different diagnostic categories and potentially advancing our understanding of the mechanisms underlying brain disorders. However, larger randomized trials are still needed to further explore the efficacy of NFB in SCZ [17].

5. Discussion

Second-generation antipsychotics have proven to be effective in dealing with positive symptoms and are less time-consuming for most patients. However, antipsychotics are not effective in treating negative and cognitive symptoms. Also, since it is a standardized medication, there is a lack of personalization.

For GENUS, this technique needs more future investigations to prove its effectiveness. For EEG Neurofeedback, the advantage is that it proved to be effective in improving the working memory test performance of the participants. However, this approach is more resource-intensive as it requires participants to attend in-person training sessions and necessitates professional monitoring of their neurofeedback training.

6. Conclusion

Four innovative nonpharmacological methods have been discussed and analyzed in this review: ECT, rTMS, GENUS, and neurofeedback training through EEG. Multiple studies have shown their effectiveness in treating some aspects of schizophrenia, but more future studies are needed. Schizophrenia is a complicated disorder that has been studied for over a century. With the improvement in technology and understanding of the neurological and genetic basis of this disorder, more unconventional but promising treatments appear. There is a large demand for efforts to prove the effectiveness of these new treatments. It is anticipated that more personalized and comprehensive treatments will be implemented for the population of schizophrenia patients in order to enhance their quality of life, as well as to advance scholars' understanding of the deeper secrets of the dorsolateral prefrontal cortex of the brain. However, this paper lacks data collection and does not include every innovative nonpharmacological treatment that is currently applied. In future studies, the author will delve deeper into such investigations and complete this study.

References

[1] Tandon, R., Nasrallah, H., Akbarian, S., Carpenter, W. T., DeLisi, L. E., Gaebel, W., Green, M. F., Gur, R. E., Heckers, S., Kane, J. M., Malaspina, D., Meyer-Lindenberg, A., Murray, R., Owen, M., Smoller, J. W., Yassine, W., & Keshavan, M. (2023). The schizophrenia syndrome,

circa 2024: What we know and how that informs its nature. Schizophrenia Research, 264, 1–28. https://doi.org/10.1016/j.schres.2023.11.015

[2] Miyamoto, S., Miyake, N., Jarskog, L. et al. Pharmacological treatment of schizophrenia: a critical review of the pharmacology and clinical effects of current and future therapeutic agents. Mol Psychiatry 17, 1206–1227 (2012). https://doi.org/10.1038/mp.2012.47

[3] Robert Freedman, Lawrence E. Adler, Greg A. Gerhardt, Merilyne Waldo, Neil Baker, Greg M. Rose, Carla Drebing, Herbert Nagamoto, Paula Bickford-Wimer, Ronald Franks, Neurobiological Studies of Sensory Gating in Schizophrenia, Schizophrenia Bulletin, Volume 13, Issue 4, 1987, Pages 669–678, https://doi.org/10.1093/schbul/13.4.669

[4] Nakamura, T., & Takata, A. (2023). The molecular pathology of schizophrenia: an overview of existing knowledge and new directions for future research. Molecular Psychiatry. https://doi.org/10.1038/s41380-023-02005-2

[5] Goldman-Rakic, P. S., & Selemon, L. D. (1997). Functional and Anatomical Aspects of Prefrontal Pathology in Schizophrenia. Schizophrenia Bulletin, 23(3), 437–458. https://doi.org/10.1093/schbul/23.3.437

[6] Barbey, A. K., Koenigs, M., & Grafman, J. (2013). Dorsolateral prefrontal contributions to human working memory. cortex, 49(5), 1195-1205. https://doi.org/10.1016/j.cortex.2012.05.022

[7] Callicott, J. H. (2000). Physiological Dysfunction of the Dorsolateral Prefrontal Cortex in Schizophrenia Revisited. Cerebral Cortex, 10(11), 1078–1092. https://doi.org/10.1093/cercor/10.11.1078

[8] Smucny, J., Dienel, S. J., Lewis, D. A., & Carter, C. S. (2022). Mechanisms underlying dorsolateral prefrontal cortex contributions to cognitive dysfunction in schizophrenia. Neuropsychopharmacology, 47(1), 292-308.

[9] McDonald C, Murphy KC. The new genetics of schizophrenia. Psychiatr Clin North Am. 2003;26(1):41–63.

[10] Ahmed, G.K., Ramadan, H.KA., Elbeh, K. et al. The role of infections and inflammation in schizophrenia: review of the evidence. Middle East Curr Psychiatry 31, 9 (2024). https://doi.org/10.1186/s43045-024-00397-7

[11] Andreasen, N. C. (1987). The Diagnosis of Schizophrenia. Schizophrenia Bulletin, 13(1), 9–22. https://doi.org/10.1093/schbul/13.1.9

[12] Patel, K. R., Cherian, J., Gohil, K., & Atkinson, D. (2014). Schizophrenia: overview and treatment options. P & T : a peer-reviewed journal for formulary management, 39(9), 638–645.

[13] Grover, S., Sahoo, S., Rabha, A., & Koirala, R. (2019). ECT in schizophrenia: a review of the evidence. Acta Neuropsychiatrica, 31(3), 115–127. doi:10.1017/neu.2018.32

[14] Arielle D. Stanford, Zafar Sharif, Cheryl Corcoran, Nina Urban, Dolores Malaspina, Sarah H. Lisanby, rTMS strategies for the study and treatment of schizophrenia: a review, International Journal of Neuropsychopharmacology, Volume 11, Issue 4, June 2008, Pages 563–576, https://doi.org/10.1017/S1461145707008309

[15] Mehta, D. D., Siddiqui, S., Ward, H. B., Steele, V. R., Pearlson, G. D., & George, T. P. (2024). Functional and structural effects of repetitive transcranial magnetic stimulation (rTMS) for the treatment of auditory verbal hallucinations in schizophrenia: A systematic review. Schizophrenia Research, 267, 86-98.

[16] Black, T., Jenkins, B. W., Laprairie, R. B., & Howland, J. G. (2024). Therapeutic Potential of Gamma Entrainment Using Sensory Stimulation for Cognitive Symptoms Associated with Schizophrenia. Neuroscience & Biobehavioral Reviews, 105681. https://doi.org/10.1016/j.neubiorev.2024.105681

[17] Singh, F., Shu, I-Wei., Hsu, S.-H., Link, P., Pineda, J. A., & Granholm, E. (2020). Modulation of frontal gamma oscillations improves working memory in schizophrenia. NeuroImage: Clinical, 27, 102339. https://doi.org/10.1016/j.nicl.2020.102339