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Review Article: The Efficacy of Neurofeedback Treatment on Positive and Negative Symptoms in Schizophrenia: A Systematic Review

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ABSTRACT

Schizophrenia is a complex and severe psychotic disorder characterized by positive symptoms (delusions, hallucinations, and disorganization of thought and behavior), negative symptoms (diminished emotional expression, avolition, alogia, anhedonia, and asociality) and significant cognitive defects (memory, executive function, and attention). Despite optimal pharmacological treatments, up to one-half of the schizophrenia patients remain relatively or actively psychotic. Although, new progresses in computational neurobiology have enhanced interest in neurofeedback (NF), a form of self-regulation or neuromodulation, in potentially decreasing cognitive symptoms in schizophrenia patients. In this systematic review, we investigated the effectiveness of NF on positive and negative symptoms in schizophrenia patients by reviewing the current body of researches. Following the PRISMA guidelines, databases were searched from inception through to 30 April 2023. We identified 13 studies (including a total of 209 schizophrenia cases and 70 controls) that met inclusion criteria, of which 6 used the electroencephalography NF (EEG NF), 5 used the real-time functional magnetic resonance imaging NF (rt-fMRI NF), one of the studies used hemoencephalography (HEG) and one study used functional near-infrared spectroscopy (fNIRS). Our results indicated that NF studies until now comprised of case studies and small sample, single-group studies, and a few randomized clinical trials. In summary, the different NF approaches are feasible and lead to measurable changes in brain function and symptoms improvement. The future studies need to be larger, randomized clinical trials and testing the efficacy of NF comparing well thought out placebos. These interventions may lead to innovative solutions that address refractory symptoms and improve daily function in schizophrenia patients.

Introduction

Schizophrenia, as a complex and severe psychotic disorder, is known with impaired functions across multiple dimensions, including cognition, language, movement, emotion, and social behavior (1). Schizophrenia affects nearly 1% of the global population and imposes considerable burdens on patients, families, and society (2, 3). The ratio of individuals with onset of schizophrenia-

spectrum disorders before the ages of 14, 18, and 25 are 3%, 12.3%, and 47.8%, respectively, with a peak at age 20.5 years (4). The clinical characteristics of schizophrenia are generally divided into two symptom domains including positive symptoms and negative symptoms (5). Schizophrenia patients experience "positive" psychotic symptoms based on the diagnostic criteria and comprise delusions, hallucinations, and disorganization of thought and behavior. The "negative" symptoms (i.e. diminished emotional expression, avolition, alogia, anhedonia, and asociality) are defined as a deficiency or loss of normal functions and behavior, reflecting the pathology which Kraepelin explained as a weakening of the well-spring of volition lead to emotional dullness and loss of drive for vocation (6). Negative symptoms divided into 2 aspects, one involving reduction of emotional expression and the second involving loss of motivation (5, 7).

Positive symptoms may result in violent behavior and affect patients' social interactions and daily functioning which are also related to social stigma and a high hospitalization rate (8). Moreover, negative symptoms may occur at any stage in schizophrenia (9). Prior researches have illustrated that negative symptoms play an important role in and contribute greatly to inability in schizophrenia patients. In addition, positive and negative symptoms not only influence patients themselves, but also the families who take care of these patients suffer from the heavy burden (8, 9).

Despite optimal pharmacological treatments, up to one-half of the schizophrenia patients remain relatively or actively psychotic. Those patients required to take different rehabilitation programs. The treatment of schizophrenia is challenging and should apply various psychosocial interventions in addition to the use of medications. Looking for new, neurofeedback (NF) has emerged as a possible novel treatment and rehabilitation option (10). NF allows patients to actively perceive and response, as well by operant conditioning, allows patients to modulate their own neural activity (11). This result in training of cognitive functions and, consequently, to the social rehabilitation. Previous studies proved the effective effects of NF, not only in treating schizophrenia (12) but also to other mental diseases, like anxiety and mood disorders (13), suicidal risk (14), attention-deficit hyperactivity disorder (ADHD) (15), and etc (16).

There are several procedures to record brain activity during NF, each has advantages and disadvantages. In electroencephalography NF (EEG NF), as a noninvasive technique, electrodes are located on a patient's scalp to diagnosis electrical activity made by the brain, which is presented on a computer screen (17). Real-time functional magnetic resonance imaging NF (rt-fMRI NF), as another approach, shows brain activity by evaluating blood oxygen-level dependent (BOLD) responses in the brain, where BOLD increases in areas of brain activity (18). EEG and rt-fMRI are the common NF methods; some other procedures have been used in a few researches. For example, functional near-infrared spectroscopy (fNIRS) measures the metabolic activity of neurons by evaluating differences in oxygenated and deoxygenated hemoglobin (19). As another approach, hemoencephalography (HEG) use infrared light to assess local blood flow in the skull (20). Regardless of the techniques applied, the principle of NF is the same.

Therefore, the aim of this systematic review was to assess the effectiveness of NF on positive and negative symptoms in schizophrenia patients by reviewing the current body of research.

Methods

Search strategy & Study selection

We were in this study followed the search strategy for systematic review and meta-analysis which presented by Moher in 2009 (21). After determine adequate key words and appropriate strategy for each selected database, all article published until 30 April 2023 in web of science, PubMed ,Scopus, ProQuest , Eric, science direct were selected. As well as other

prestigious journals in the field were visited. The search strategy includes "(neurofeedback)" AND "schizophrenia". This produced 572 articles published from 1990 to 2023. Of these 572 articles, 248 were excluded because of duplicates records. 324 articles screened by title and abstract and 163 were excluded due to no relevant subject. Then, 161 full-text articles assessed for eligibility. Finally, 148 full-text articles excluded, because of no relevant comparison, no relevant outcomes, non-relevant study design, non-English language full text, and no assessment of positive and negative symptoms. Only 13 studies met inclusion criteria (**Figure 1**: PRISMA flowchart). In the final step, in order to assessment the quality of 13 selected papers, the Mixed Methods Appraisal Tool (MMAT) – Version 2011 was used. The reason for choosing this tool was that the selected articles had different methodologies, so we used this tool whose validity and effectiveness were verified in a study by Pace in 2011 (22) and also a study by Pluye in 2014 (23). For all studies, methodological quality ranged from 25 – 100% (good quality).

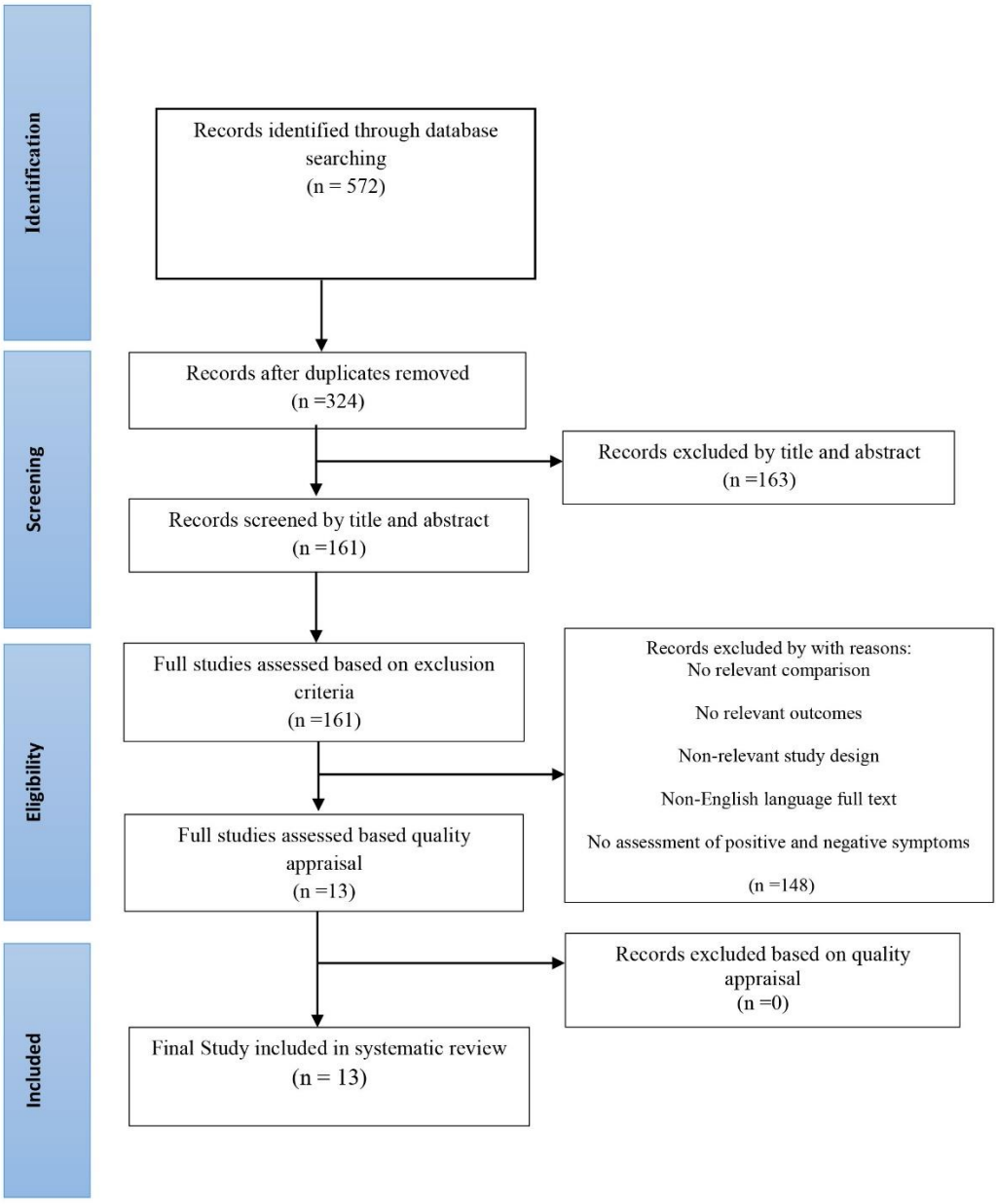

Figure1. PRISMA 2009 flow diagram. From Moher et al.

Table 1. Inclusion & exclusion criteria.

Parameter	Inclusion criteria	Exclusion criteria
Population	Schizophrenia	Healthy individuals only
Intervention	Neurofeedback	Other treatment
Comparator	Schizophrenia patients, healthy persons, control group	-
Outcomes	Improvement in positive and negative symptoms	Not adequately described outcomes
Study design	Randomized clinical trials, cross sectional, proof-of-concept studies, case studies	Review articles

The patients, intervention, comparator, outcomes, study design (PICOS) criteria for inclusion and exclusion of studies are presented in **Table 1**.

Data collection and data items

The data extraction and synthesis of study results was done by peer review team. Peer review team involved two authors which independently assessing articles, then gaining a consensus over the final study through debate.

We read each study several times to master the research context, finding and inferences. The extracted data consist of research methodology, study design, study sample, study location, purpose, year, average age, type of NF method, duration of intervention, and main outcomes.

Results

The included studies involved 279 participants: 209 schizophrenia patients and 70 mental health persons. Also, 64.1% of participants were male and the mean age was 35.6 years. The highest number of participants was reported in the study done by Markiewicz et al. (24) in Poland (60 patients) and the lowest was in the case study performed by Storchak et al. (25) in Germany (1 patient) and another case study by Nan et al. (26) in China (1 patient). Years of publications ranged between 1992 and 2021. In terms of the study location, the most studies were conducted in Germany (4 studies); and other were done in Italy, Turkey, China, Austria, England, America, Brazil, Poland and Switzerland. Of the 13 studies, 6 used the EEG NF, 5 used the rt-fMRI, one of the studies used HEG and one study used fNIRS.

EEG NF in Treatment of schizophrenia

Of the 6 EEG NF studies, 2 were case studies. One study used EEG and fNIRS to record brain changes in patients. EEG NF treatment dose ranged from 3.75 hours to 58.5 training hours.

In 1992, Schneider et al. (27) from America used EEG NF to target slow cortical potentials (SCPs), which are supposed to reflect regulation of the brain's attention resources and cortical excitability. Attention defects are well defined in schizophrenia, thus, they thought that improved self-regulation of SCPs might result in symptom reduction. 12 schizophrenia patients and 12 healthy persons were included in the study. Patients were received antipsychotic medications during the study period. Scalp electrical recordings from electrode site were used for SCPs monitoring. Participants were needed to either increase or decrease SCP during 20 EEG NF sessions (nearly 4.89 h of NF). Their findings showed that the schizophrenia patients learned to control SCPs at a slower rate comparing the healthy persons. Moreover, those with severe symptom reported learning reduction.

In 2012, Surmeli et al. (28) in Turkey used quantitative EEG NF (qEEG NF) on 51 schizophrenia patients (25 male and 26 female) to normalize brain activity in deviating regions. Because schizophrenic patients decrease alpha activity and increase beta activity, or negative symptoms are associated with an increase in delta activity in the temporal region. Patients averagely done 58.5 one-hour qEEG NF sessions across the period of 24–91 days. Before recording baseline qEEG, patients discontinued antipsychotic medications, which the first EEG was started after 7 half-lives of discontinue

Table 2. Neurofeedback Treatment Studies in Patients with Schizophrenia

Authors	Year	Country	Sample	NF Modality	Protocol	Treatment Dose (h)	Control	Outcomes
Markiewicz	2021	Poland	60	qEEG	24 qEEG NF sessions over the course of 3 months	-	schizophrenia patients	Significant improvement on the PANSS, the NF group was more able to cope with stressful or difficult social situations.
Zweerings	2019	Germany	56	rt-fMRI	8 NF sessions, left anterior IFG and left posterior STG activity	0.56 h	healthy persons	post-treatment behavioral improvement, and decreased symptom severity
Storchak	2018	Germany	1	fNIRS	47 NF sessions, activity in STG during AVH, and activity in STG before AVH	-	-	Significant reduction in AVH according to the PANSS and PsyRats tests
Orlov	2018	England	12	rt-fMRI	4 NF sessions, regulate voice-sensitive regions in left STG	1.93 h	-	In the psychotic rating symptoms scale (PsyRats), there was a decrease in item 5 (beliefs about the origin of sounds) and item 9 (severity of distress). The mood (PANAS) was not changed.
Balconi	2018	Italy	18	EEG	10 NF sessions, power in .5–5.5 Hz (delta/low theta) to treat hemispheric imbalance	3.75 h	schizophrenia patients	The NF group rated negative IAPS Pictures as more positive at post-treatment
Pazooki	2018	Austria	2	EEG	20 NF sessions, (SMR, 12–15 Hz), and inhibiting theta (4–8 Hz)	10 h	-	significant improvements of negative symptoms
Gomes	2018	Brazil	20	HEG	10 NF sessions, activity at F7, Fp1, Fp2, and F8	1 h	healthy persons	Both groups improved the most aspects of cognitive function. No significant difference was found in terms of positive and negative symptoms.
Nan	2017	china	1	EEG	12.5 h of NF	12.5 h	-	both negative and positive symptom severity improved significantly at 22 months post completing NF
Dyck	2016	Germany	3	rt-fMRI	9 NF sessions, ACC activation	1.28 h	-	Mood (PANAS) improved during rt-fMRI NF training
Cordes	2015	Germany	22	rt-fMRI	3 NF sessions, ACC activation	1.28 h	healthy persons	Experimental group activity in dorsal ACC, healthy subjects activity in rostral ACC

Table 2 continue

Ruiz	2013	Germany	9	rt-fMRI	12 NF sessions, activation of bilateral insular cortex	1.30 h	-	Improved control of anterior insula cortex: better control of negative symptoms
Surmeli	2012	Turkey	51	EEG	Average of 58.5 h of NF, targeting deviations in individual qEEG	58.5 h	-	Considerable improvement on the PANSS
Schneider	1992	America	24	EEG	20 NF sessions, regulate activity of SCP	4.89 h	healthy persons	Experimental group required more NF training to achieve similar control of SCP compared to healthy controls

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medication. qEEG NF training led to considerable improvement on the Positive and Negative Syndrome Scale (PANSS). Also, 19 participants had normal brain activity after qEEG NF treatment and at a 22 month follow-up, 27 participants remained medication-free.

In 2017, Nan and coworkers (26) in china conducted intensive EEG NF on a 51-year-old woman who suffering from chronic schizophrenia with auditory verbal hallucinations (AVHs) since 7 years ago and has not respond to medication. During 4 consecutive days, the patient completed 12.5 hours of EEG NF along with medications. The results illustrated that both negative and positive symptom severity improved significantly at 22 months post completing NF.

In a case study of 2 patients in 2018, Pazooki et al. (29) in Austria assessed the use of EEG NF for the treatment of negative symptoms related to schizophrenia. Both patients continued the antipsychotic medications as usual and no changes were occurred. Given that negative symptoms may be nearly responsible for reduced attention, the NF protocol aimed to enhance sensorimotor rhythm (SMR, 12–15 Hz), and inhibiting theta (4–8 Hz), both are related to attention in schizophrenia. Both patients received 20 thirty-minute NF sessions. EEG NF training resulted in significant improvement of the ability to regulate alpha, beta, theta, and SMR activity and also, negative symptoms.

In 2018, Balconi and colleagues (30) in Italy targeted to improve emotion regulation in schizophrenia patients utilizing EEG NF and fNIRS. Patients were divided into 2 groups: the treatment group including 9 schizophrenia patients who received NF (n = 9) and the control group comprising 9 schizophrenia patients who received treatment as usual. The treatment group received 10 twenty five-minute NF sessions. Pre-post testing consisted of (1) emotion recognition of 40 negative, 40 positive, and 20 neutral International Affective Picture System (IAPS) images. Next, patients rated each picture for valence and arousal while EEG and fNIRS were reported and (2) Self-Assessment Manikin (SAM) rating of emotional experience. Their findings demonstrated that the NF group rated negative IAPS Pictures as more positive at post-treatment.

In 2021, Markiewicz et al. (24) in Poland used qEEG NF on 60 schizophrenia patients (all were male) to improve their clinical, cognitive, and psychosocial status. Patients were divided into 2 groups (30 people for each group). Patients received 24 qEEG NF sessions over the course of 3 months. qEEG NF training caused to significant improvement on the PANSS. The NF group was more able to cope with stressful or difficult social situations. Finally, they concluded that NF can be effectively used as an additional treatment in schizophrenia rehabilitation programs.

rt-fMRI NF in Treatment of schizophrenia

Five of the studies included in this systematic

review used rt-fMRI NF (**table 2**). Of the 5 EEG NF studies, one was case study. The number of rt-fMRI NF sessions was ranging from 3 to 10, and the length of each session was ranging from 4 to 54 min.

In 2013, Ruiz et al. (31) in Germany used rt-fMRI NF on 9 schizophrenia patients (4 male and 5 female) to affect activation of bilateral insula cortex (BIC). They choose the insula because of its role in emotion recognition. The patients continued the antipsychotic medications as usual. Patients done three scanning sessions of self-regulation training in 2 days per week across the period of 2 weeks (12 sessions). After NF treatment, patients reported elevated activation of BIC. Likewise, they indicated enhanced recognition of "disgust" faces, and reduced recognition of "happy" faces on the emotion identification task. also, negative association between insular activation and negative symptoms was reported showing which much severe negative symptoms are correlated with difficulties to learn self-regulation.

In 2015, Cordes and colleagues (32) in Germany assessed the utilization of rt-fMRI NF to target upregulation of anterior cingulate cortex (ACC) activation. 11 schizophrenia patients and 11 healthy persons were included in the study. The patients continued the antipsychotic medications as usual. Since cognitive function is damaged in schizophrenia and ACC has a central role in cognitive processing, the ACC was chosen with the aim of treating cognitive defects. Patients received 3 sessions of rt-fMRI NF across the period of 1 week (nearly 1.28 hours). Both groups were successful in upregulating ACC activity post-treatment, although by using difference that schizophrenia patients activated the dorsal part of the ACC and the healthy persons activated the rostral (serial) part of the ACC. Needless to say, the authors did not present any data about behavior pre/post NF as an important limitation.

In 2016, Dyck et al. (33) in Germany conducted rt-fMRI NF to upregulate ACC activation (1.28 h, 9 sessions i.e. 3 sessions over 3 days) in 3 schizophrenia patients suffering from AVH. The effect of rt-fMRI NF training on hallucinations' severity was measured using the Auditory Vocal Hallucination Rating Scale (AVHRS) and on the emotional situation with the PANAS. Considerable upregulation of the ACC was reported in all 3 patients. Some aspects of AVHs (AVHRS) like disorder and suffering from the voices were improved. Totally, mood (PANAS) improved during rt-fMRI NF training; however two patients showed worse mood post treatment.

In 2018, Orlov and colleagues (34) in England used rt-fMRI NF in 12 schizophrenia patients with treatment-resistant auditory hallucinations to downregulate activity in the left superior temporal gyrus (STG), a node in the left-hemispheric language network. The patients were received their usual antipsychotic treatment. Patients received 4 sessions of rt-fMRI NF during 2 weeks (about 2 hours). The results observed that rt-fMRI NF remarkably improved the patient's ability to (1) downregulate left STG activation, and (2) enhance functional connectivity between Inferior Frontal Gyrus (IFG), STG, and inferior parietal cortex. This demonstrated an elevated connectivity in the speech motor and speech perception regions of the language network. In the psychotic rating symptoms scale (PsyRats), there was a decrease in item 5 (beliefs about the origin of sounds) and item 9 (severity of distress). But, the mood (PANAS) was not changed.

In Germany, Zweerings et al. (35) (2019) performed rt-fMRI NF to assess left-hemispheric language nodes in 21 schizophrenia patients with AVH and 35 healthy persons. The patients continued the antipsychotic medications as usual. All patients took feedback to up- or downregulate in 2 regions of interest for nearly 0.5 h. the IFG and posterior STG, two nodes in the left-hemispheric language network, were chosen as main locations. The improved self-regulation in these regions might cause to AVH decreasement. Their findings indicated that higher coupling between language nodes and the default mode network post treatment, with greater functional connectivity in the

schizophrenia group than healthy persons. Furthermore, post-treatment behavioral improvement was related to elevated functional coupling between the left IFG and left inferior parietal lobe (IPL) in schizophrenia patients.

fNIRS and HEG NF in Treatment of schizophrenia

In 2018, Gomes et al. (36) in Brazil assessed the utilization of HEG NF training to improve cognitive defects in 8 schizophrenia patients with an average IQ of 95 comparing to 12 healthy controls with an average IQ of 113 during 10 sessions (1 hour). Patients took HEG NF twice a week at the 4 frontal electrode places F7, Fp1, Fp2, and F8 to improve prefrontal cortical function. Post treatment, the left-hemispheric sites (F7 and Fp1) indicated notably higher activity in both groups, and the right F8 site reported relatively remarkable change. Both groups improved the most aspects of cognitive function (speed of processing, working memory, verbal memory, visual learning, and executive function). No significant difference was found between pre and post treatment in terms of positive and negative symptoms.

In a case study, Storchak and colleagues (25) in 2018 investigated the use of fNIRS to treat severe AVH in a woman with paranoid schizophrenia in Germany. The patient continued the antipsychotic medications as usual. FNIRS measures the metabolic activity of neurons by measuring oxygenated and deoxygenated hemoglobin around the neurons. Patient done 47 fNIRS NF sessions targeting activation in the bilateral posterior STG, a speech-activated place which play role in AVH. After 47 NF sessions, there was a significant reduction in AVH according to the PANSS and PsyRats tests.

Discussion

Schizophrenia is a mental disease that affects approximately 1% of the population. Recent research has focused much attention on the neurological changes responsible for the schizophrenia symptoms, including the gray and white matter reduction. For example, AVHs is associated with anatomical changes in the STG as well as structural and functional abnormalities in other areas involved in auditory perception, such as the primary and secondary auditory cortex (7). One of the causes of this disease is brain damage, mainly damage to the frontal lobes; the main symptoms of this disease are divided into two categories, positive and negative symptoms. Positive symptoms are symptoms that did not exist in the person before but now exist and usually cause distortion in normal functioning. These symptoms include hallucinations, delusions, irrelevant and illogical behavior and speech (5). Crowe believed that these symptoms are caused by chemical defects in the brain's dopamine systems. Negative symptoms include behaviors, emotions, feelings, or thought processes that normally exist but are not present in these person or that are reduced, such as superficial emotion, blocking of thought, apathy, social isolation, lack of eye contact According to Crowe, the cause of these disorders is the loss of brain tissues (37).

NF has emerged as a new treatment option. NF through operant conditioning, allows patients to modulate their neural activity. There are several different methods for recording brain activity during NF, each with its own advantages and disadvantages. Regardless of the technique used, the principle of NF is the same. Therefore, this systematic review was aimed to assess the effectiveness of NF on positive and negative symptoms in schizophrenia patients.

The review of studies showed that although the principles of NF are the same, it has been used in various protocols in schizophrenia. Furthermore, despite the large number of published studies related to NF, there are currently few studies with empirical data in the literature. Despite these limitations, NF appears to affect neural processing, communication centers, and metabolism in the brain, as shown by changes in scalp electrical activity before and after and neuroimaging studies. Some studies with longer follow-up periods have found

evidence of persistent brain changes even months after the training ends.

The present study found that rt-fMRI protocols reach efficiency in a shorter period compared to EEG, however, the cost, inconvenience and expensive equipment of rt-fMRI may prevent its use as a clinical intervention widely. Given the ease of use and potential efficacy of HEG in a shorter protocol, this method should benefit from further testing in larger samples. In general, due to the flexibility and variety of neurofeedback treatment protocols (alpha, beta, delta, gamma, and theta) and different EEG electrode locations (temporal, central, occipital, unipolar, and bipolar), it can easily be included in a more customized or personalized treatment intervention for disorders that are complex and different in terms of symptoms.

In the meta-analysis conducted by Fusar et al. in 2015, 168 clinical trial studies for assessing the effectiveness of different treatments on the negative symptoms of schizophrenia were reviewed until December 2013. Various treatments including second-generation antipsychotics, antidepressants, combinations of pharmacological agents, glutamatergic drugs, and psychological interventions reduced negative symptoms at follow-up comparing to placebo, but no significant effect was found for first-generation antipsychotics and brain stimulation. Although some statistically significant effects on negative symptoms were evident, none reached the threshold of clinically significant improvement. This suggests that although most treatments appeared to have a statistically significant effect on negative symptoms, the effect was not large enough to be clinically meaningful. The lack of clinically meaningful efficacy is consistent with the experience of clinicians in practice who do not find any available treatment useful for negative symptoms. While there are well-established models of positive psychotic symptoms that can be used as a rational basis for pharmacological and psychological treatments (38).

Also, in another systematic review study, Veerman et al. evaluated the treatment of negative symptoms in schizophrenia patients. They indicated that there was no convincing evidence of efficacy for the treatment of initial and persistent negative symptoms. However, for several interventions there is short-term evidence of effectiveness on negative symptoms. This evidence is mainly derived from studies conducted on chronically patients and studies with heterogeneous populations. Did not provide reliable information on the distinction between primary and secondary negative symptoms. They also showed that early treatment of psychosis, adjunctive treatment with aripiprazole, antidepressants, music therapy and exercise are beneficial for negative symptoms of schizophrenia (39).

In a systematic review, Lutgens et al investigated psychological and psychosocial interventions effective in reducing the negative symptoms of schizophrenia. A total of 95 studies with a high level of heterogeneity were reviewed. Compared to usual treatment, cognitive-behavioral therapy, skill-based training, exercise, and music therapy showed significant benefits in reducing negative symptoms of schizophrenia. They also concluded that specific psychological and psychosocial interventions are useful in improving negative symptoms in psychosis and should be included in the treatment of negative symptoms of schizophrenia. However, more effective treatments for negative symptoms need to be developed (40).

In the meta-analysis conducted by Riehle et al., the effectiveness of psychological treatments for patients with schizophrenia and negative symptoms was investigated. They showed that both cognitive behavioral therapy and cognitive remediation performed better than treatment-as-usual in reducing negative symptoms, and there was no difference between cognitive behavioral therapy and cognitive remediation. Although the effects of these approaches are promising, high-quality trials testing psychological treatments for negative symptoms are needed to place treatment recommendations on a

sufficiently firm basis (41).
Also, for the effect of antipsychotic drugs for patients with schizophrenia and dominant or prominent negative symptoms, Krause et al. investigated 21 randomized and controlled trials. They showed that in patients with predominant negative symptoms, amisulpride was superior to placebo, olanzapine was superior to haloperidol in a small trial, and cariprazine was superior to risperidone. In patients with prominent negative symptoms, olanzapine and quetiapine were superior to risperidone in some trials. They also showed that amisulpride is the only antipsychotic that worked better than placebo in treating dominant negative symptoms, and a parallel reduction in depression was also observed (41).

Conclusion

Our results indicated that NF studies until now comprised of case studies and small sample, single-group studies, and a few randomized clinical trials. In summary, the different NF approaches are feasible and lead to measurable changes in brain function and symptoms improvement. The future studies need to be larger, randomized clinical trials and testing the efficacy of NF comparing well thought out placebos. These interventions may lead to innovative solutions that address refractory symptoms and improve daily function in schizophrenia patients.

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Conflicts of interest

The authors declare no conflict of interest.

Authors' contributions

All authors were involved in the conception and design, analysis and interpretation of the data, drafting of the manuscript and revising it critically for intellectual content, approved the final version for submission, and agreed to be accountable for all aspects of the work.

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References

1. Kaufmann T, Skåtun KC, Alnæs D, Doan NT, Duff EP, Tønnesen S, et al. Disintegration of sensorimotor brain networks in schizophrenia.Schizophr Bull.. 2015;41(6): 1326-35.
2. Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature. 2022;604(7906):502-8.
3. McCutcheon RA, Marques TR, Howes OD. Schizophrenia—an overview. JAMA psychiatry. 2020;77(2):201-10.
4. Solmi M, Seitidis G, Mavridis D, Correll CU, Dragioti E, Guimond S, et al. Incidence, prevalence, and global burden of schizophrenia-data, with critical appraisal, from the Global Burden of Disease (GBD) 2019. Molecular psychiatry. 2023; 28(12): 5319-27.
5. Marder SR, Galderisi S. The current conceptualization of negative symptoms in schizophrenia. World Psychiatry. 2017;16(1): 14-24.
6. Strauss JS, Carpenter WT, Bartko JJ. Speculations on the processes that underlie schizophrenic symptoms and signs: III. Schizophrenia bulletin. 1974;1(11):61.
7. Galderisi S, Mucci A, Buchanan RW, Arango C. Negative symptoms of schizophrenia: new developments and unanswered research questions. The Lancet Psychiatry. 2018;5(8):664-677.
8. Ruiz-Castañeda P, Santiago Molina E, Aguirre Loaiza H, Daza González MT. Positive symptoms of schizophrenia and their relationship with cognitive and emotional executive functions. Cogn Research. 2022; 7(1):1-19.

9. an der Heiden W, Leber A, Häfner H. Negative symptoms and their association with depressive symptoms in the long-term course of schizophrenia. Eur Arch Psychiatry Clin Neurosci . 2016;266(5):387-396.
10. Gandara V, Pineda JA, Shu I-W, Singh F. A systematic review of the potential use of neurofeedback in patients with schizophrenia. Schizophrenia Bulletin Open. 2020;1(1):sgaa005.
11. Markiewicz R. The use of EEG Biofeedback/Neurofeedback in psychiatric rehabilitation. Psychiatria Polska. 2017;51(6).
12. Lin C-J, Hung Y-Y, Lin C-C, Tsai M-C, Huang T-L. Does biofeedback improve symptoms of schizophrenia (emotion, psychotic symptoms, and cognitive function)? Taiwan Psychiatry. 2016;30(2):120-7+ iv.
13. Banerjee S, Argáez C. Neurofeedback and biofeedback for mood and anxiety disorders: A review of clinical effectiveness and guidelines. 2017.
14. Liu D-Y, Shen X-M, Yuan F-F, Guo O-Y, Zhong Y, Chen J-G, et al. The physiology of BDNF and its relationship with ADHD. Mol Neurobiol. 2015;52:1467-76.
15. Batail J-M, Bioulac S, Cabestaing F, Daudet C, Drapier D, Fouillen M, et al. EEG neurofeedback research: A fertile ground for psychiatry? L'encephale. 2019;45(3):245-55.
16. Dinh ST, Nickel MM, Tiemann L, May ES, Heitmann H, Hohn VD, et al. Brain dysfunction in chronic pain patients assessed by resting-state electroencephalography. Pain. 2019;160(12):2751- 65.
17. Lührs M, Riemenschneider B, Eck J, Andonegui AB, Poser BA, Heinecke A, et al. The potential of MR-Encephalography for BCI/Neurofeedback applications with high temporal resolution. Neuroimage. 2019; 194:228-43.
18. Gvirts HZ, Perlmutter R. What guides us to neurally and behaviorally align with anyone specific? A neurobiological model based on fNIRS hyperscanning studies. The Neuroscientist. 2020;26(2):108-16.
19. Serra-Sala M, Timoneda-Gallart C, Pérez-Álvarez F. Clinical usefulness of hemoencephalography beyond the neurofeedback. Neuropsychiatric Disease and Treatment. 2016:1173-80.
20. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Reprint—preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Physical therapy. 2009;89(9):873-80.
21. Pace R, Pluye P, Bartlett G, Macaulay AC, Salsberg J, Jagosh J, et al. Testing the reliability and efficiency of the pilot Mixed Methods Appraisal Tool (MMAT) for systematic mixed studies review. International journal of nursing studies. 2012;49(1):47-53.
22. Pluye P, Hong Q. Appraising qualitative, quantitative and mixed methods studies included in mixed studies reviews: The MMAT. Annu Rev Public Health. 2014;35:29-45.
23. Markiewicz R, Markiewicz-Gospodarek A, Dobrowolska B, Łoza B. Improving clinical, cognitive, and psychosocial dysfunctions in patients with schizophrenia: A neurofeedback randomized control trial. Neural Plasticity. 2021;2021 (1):4488664.
24. Storchak H, Hudak J, Haeussinger FB, Rosenbaum D, Fallgatter AJ, Ehlis A-C. Reducing auditory verbal hallucinations by means of fNIRS neurofeedback-A case study with a paranoid schizophrenic patient. Schizophr Res. 2019;204:401-3.
25. Nan W, Wan F, Chang L, Pun SH, Vai MI, Rosa A. An exploratory study of intensive neurofeedback training for schizophrenia. Behavioural neurology. 2017;2017 (1):6914216.
26. Schneider AL, Schneider TL, Stark H. Repetitive transcranial magnetic stimulation (rTMS) as an augmentation treatment for the negative symptoms of schizophrenia: a 4-week randomized placebo controlled study. Brain Stimulation. 2008;1(2):106-11.
27. Surmeli T, Ertem A, Eralp E, Kos IH. Schizophrenia and the efficacy of qEEG-guided neurofeedback treatment: a clinical case series. Clinical EEG and Neuroscience. 2012;43(2):133-44.
28. Pazooki K, Leibetseder M, Renner W, Gougleris G, Kapsali E. Neurofeedback treatment of negative symptoms in schizophrenia: two case reports. Appl

Psychophysiol Biofeedback . 2019;44:31-9.
29. Balconi M, Frezza A, Vanutelli ME. Emotion regulation in schizophrenia: A pilot clinical intervention as assessed by EEG and optical imaging (functional near-infrared spectroscopy). Front Hum Neurosci. 2018; 12:395.
30. Ruiz S, Lee S, Soekadar SR, Caria A, Veit R, Kircher T, et al. Acquired self-control of insula cortex modulates emotion recognition and brain network connectivity in schizophrenia. Hum Brain Mapp. 2013; 34(1):200-12.
31. Cordes JS, Mathiak KA, Dyck M, Alawi EM, Gaber TJ, Zepf FD, et al. Cognitive and neural strategies during control of the anterior cingulate cortex by fMRI neurofeedback in patients with schizophrenia. Frontiers in behavioral neuroscience. 2015;9:169.
32. Dyck MS, Mathiak KA, Bergert S, Sarkheil P, Koush Y, Alawi EM, et al. Targeting treatment-resistant auditory verbal hallucinations in schizophrenia with fMRI-based neurofeedback–exploring different cases of schizophrenia. Front Psychiatry. 2016;7:37.
33. Orlov ND, Giampietro V, O'Daly O, Lam S-L, Barker GJ, Rubia K, et al. Real-time fMRI neurofeedback to down-regulate superior temporal gyrus activity in patients with schizophrenia and auditory hallucinations: a proof-of-concept study. Transl Psychiatry. 2018;8(1):46.
34. Zweerings J, Hummel B, Keller M, Zvyagintsev M, Schneider F, Klasen M, et al. Neurofeedback of core language network nodes modulates connectivity with the default-mode network: a double-blind fMRI neurofeedback study on auditory verbal hallucinations. Neuroimage. 2019;189:533-42.
35. Gomes J, Ducos D, Gadelha A, Ortiz B, Van Deusen A, Akiba H, et al. Hemo-encephalography self-regulation training and its impact on cognition: A study with schizophrenia and healthy participants. Schizophr Res 2018;195:591-3.
36. Strauss GP, Nuñez A, Ahmed AO, Barchard KA, Granholm E, Kirkpatrick B, et al. The latent structure of negative symptoms in schizophrenia. JAMA psychiatry. 2018;75 (12):1271-9.
37. Fusar-Poli P, Papanastasiou E, Stahl D, Rocchetti M, Carpenter W, Shergill S, et al. Treatments of negative symptoms in schizophrenia: meta-analysis of 168 randomized placebo-controlled trials. Schizo-phrenia bulletin. 2015;41(4):892-9.
38. Veerman SR, Schulte PF, De Haan L. Treatment for negative symptoms in schizophrenia: a comprehensive review. Drugs. 2017;77(13):1423-59.
39. Lutgens D, Gariepy G, Malla A. Psychological and psychosocial interventions for negative symptoms in psychosis: systematic review and meta-analysis. The British Journal of Psychiatry. 2017;210 (5):324-32.
40. Riehle M, Böhl MC, Pillny M, Lincoln TM. Efficacy of psychological treatments for patients with schizophrenia and relevant negative symptoms: a meta-analysis. Clin Psychol Eur. 2020;2(3):e2899.
41. Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Nikolakopoulou A, et al. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci. 2018;268:625-39.