

Review Article

Effectiveness of Neurofeedback Training for Patients with Personality Disorders: A Systematic Review

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Abstract

Objective: Personality disorders are serious psychiatric conditions, and some studies have examined neurofeedback training as a potential alternative treatment to improve cognitive and clinical symptoms in patients with such disorders. Here, we aimed to provide a first systematic review of such trials and present existing evidence regarding this treatment for individuals with personality disorders.

Method: A systematic search of peer-reviewed English journal articles was conducted for this study to identify original studies on fMRI and EEG neurofeedback treatment protocols in patients with personality disorders up to January 2023. PubMed, Web of Science, ProQuest, Cochrane Library, and Google Scholar databases were queried through the keywords "neurofeedback," "biofeedback," and "personality disorder," as well as their related Mesh synonyms.

Results: Totally, five studies were included in our systematic review. Two studies utilized EEG neurofeedback protocols, while three articles used real-time fMRI neurofeedback protocols. The types of studies were non-randomized, not-blinded case reports, case series, and single-arm trials with a high risk of bias. EEG neurofeedback protocols applied more training sessions and reported improvements in patients' neuropsychological and behavioral functions after treatment. Furthermore, fMRI-based neurofeedback studies reported neurophysiological changes, such as a shift in vmPFC-amygdala connectivity, towards healthy states following treatment. Moreover, behavioral symptoms of patients were reported to be improved after fMRI neurofeedback.

Conclusion: Neurofeedback studies investigating this therapeutic technique for personality disorders are still very preliminary, and no strict conclusions can be drawn at this time. Therefore, further basic and clinical investigations are required to address several open methodological and technical questions and establish consensus and standardization, which will eventually lead to translational works.

Key words: *Neurofeedback; Personality Disorders; Self-Regulation; Systematic Review*

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Personality disorders are destructive psychiatric conditions with severe mental distress and functional deficits (1). The prevalence of personality disorders worldwide is about 7.8%, with higher rates among high-income countries (2, 3). In contrast to patients with psychiatric disorders such as depression, anxiety, and obsessive compulsive disorder, those with personality disorders are highly prone to abandoning psychological help and denying their problems (4). Psychotherapy and psychopharmacology currently serve as the standard treatments for these patients (5). However, the personality traits of these patients often hinder the proper effectiveness of these treatments. Patients with personality disorders often do not adhere adequately to their medications. Although psychotherapy is a good approach for helping these patients develop interpersonal and social skills, establishing and maintaining an adequate patient-therapist relationship for patients with personality disorders poses significant challenges because of their unstable emotions, anger, impulsivity, and poor interpersonal skills (6, 7). Therefore, finding an optimal treatment to alleviate the symptoms of personality disorders has remained a hot research topic in psychiatry and psychology.

The neuropsychiatry literature reveals that personality disorders have been linked to dysfunction in brain regions, including frontal cortex, amygdala, and anterior cingulate cortex, which are associated with clinical symptoms such as affective instability, emotion dysregulation, impulsivity, and severe interpersonal distress (8, 9). Previous research has shown that individuals with impulsive aggression exhibit disturbances in the neural circuits that modulate emotions (10). The amygdala, an almond-shaped structure located in the medial temporal region, is a critical structure of the brain network that modulates social behavior and negative emotions (11). In fact, the cognitive regulation of emotions depends on amygdala activity (12). On the other hand, the prefrontal cortex plays an important role in regulating emotions and maintaining overall mental health (13). The neural connection between the prefrontal cortex and the amygdala is the main neural pathway for emotion regulation (14), and abnormal prefrontal-amygdala connectivity has been suggested as a neural correlate of emotion dysregulation in personality disorders (15, 16). Therefore, this abnormality has been the target of neurofeedback-based real-time therapies as alternative and adjunctive treatments for personality disorders.

Neurofeedback is a therapeutic method that provides real-time visual or auditory feedbacks to subjects regarding their neural self-regulation function (17). Feedbacks are usually originated from brain regions that are hypothesized to be the neural substrates of specific pathologies or behaviors (18). For example, a common symptom in personality disorders is emotion dysregulation, possibly due to the hyperactivation of the

amygdala in response to emotional stimulation (15). Thus, previous neurofeedback studies have treated patients with personality disorders based on this neuropathology (19). Electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) were neuroimaging methods used to instruct self-regulation in patients with personality disorders. EEG is an electrophysiological method that measures the local field potential, providing a direct measurement of neuronal activities through scalp electrodes. In contrast, fMRI measures the blood oxygen level dependent (BOLD) signal as an indirect measurement of neuronal activities (20). Regardless of the neuroimaging method, neurofeedback training typically involves three major steps: (1) defining a neural target based on putative neuropathology, (2) recording and analyzing the activity of this neural target, and (3) providing real-time feedbacks of neural function to the subject (21). Such real-time feedbacks enable the patient to develop, modify, and optimize a behavioral or mental control approach, thereby achieving an optimal level of skill in the self-regulation of neurophysiological activities (22).

Neurofeedback protocols are typically designed based on computational or neurophysiological models that have been proposed to elucidate the genesis of a psychiatric condition. As a result, this approach enables us to directly examine the causal validity of proposed neuropathologies and biomarkers (23). Furthermore, unlike brain stimulation methods, such as transcranial magnetic stimulation and transcranial direct current stimulation, neurofeedback is an endogenous neuromodulator, thereby mitigating important issues regarding side effects and safety. In this endogenous, non-invasive approach, the patient is an active participant in the intervention and may benefit from the positive psychosocial and psychophysiological effects it offers (24). Accordingly, some studies in recent years have sought to investigate the effects of neurofeedback therapy on cognitive and clinical symptoms of personality disorders. However, no systematic review has yet summarized these studies. Given the increasing number of neurofeedback studies for treating psychiatric disorders and the importance of investigating the effectiveness of this treatment for personality disorders, we aimed to: (1) summarize and compare existing observations, (2) assess the quality of these trials, and (3) suggest future directions to pave the way for further research in this field.

Materials and Methods

Design

A systematic search of peer-reviewed English journal articles published up to 18 January 2023 was conducted for this study to find original studies on fMRI and EEG neurofeedback treatment protocols in patients with personality disorders. PubMed, Web of Science, ProQuest, Cochrane Library, and Google Scholar databases were queried using the keywords "neurofeedback," "biofeedback," and "personality

disorder" as well as their related Mesh synonyms. We selected original articles (different types of trials or case reports) that included human subjects with formally diagnosed personality disorders. Conversely, we excluded articles lacking participants with personality disorders, those employing biofeedback based on non-neural protocols, and animal studies and articles providing a review, commentary or editorial.

Study selection, data extraction and quality assessment

Two researchers screened the articles based on their titles and abstracts and discussed them in case of disagreement. To gather related information, a data extraction form was developed to extract important items in different categories, including research design (participants, diagnostic criteria, blinding, randomization, control condition, training protocol, and assessment times, and outcome measures), and main outcomes (within-group differences, between-group differences, and follow-up

results). The Consensus Checklist on Reporting and Experimental Design of Neurofeedback studies (CRED-nf) has recently been published to propose essential and suggested issues regarding the design and reporting of trials (25). Here, we used this checklist to assess the quality of the included studies. The qualitative evaluation was carried out independently by two researchers, and any disagreements were resolved by discussing them.

Results

As depicted in Figure 1, a total of 603 papers were identified in the five mentioned databases, and an additional six articles were found from the reference lists of the included studies. Out of the total, 592 articles were rejected either due to duplication issues or failure to meet our inclusion criteria. Following full-text check, only five studies (26-30) were included in our systematic review.

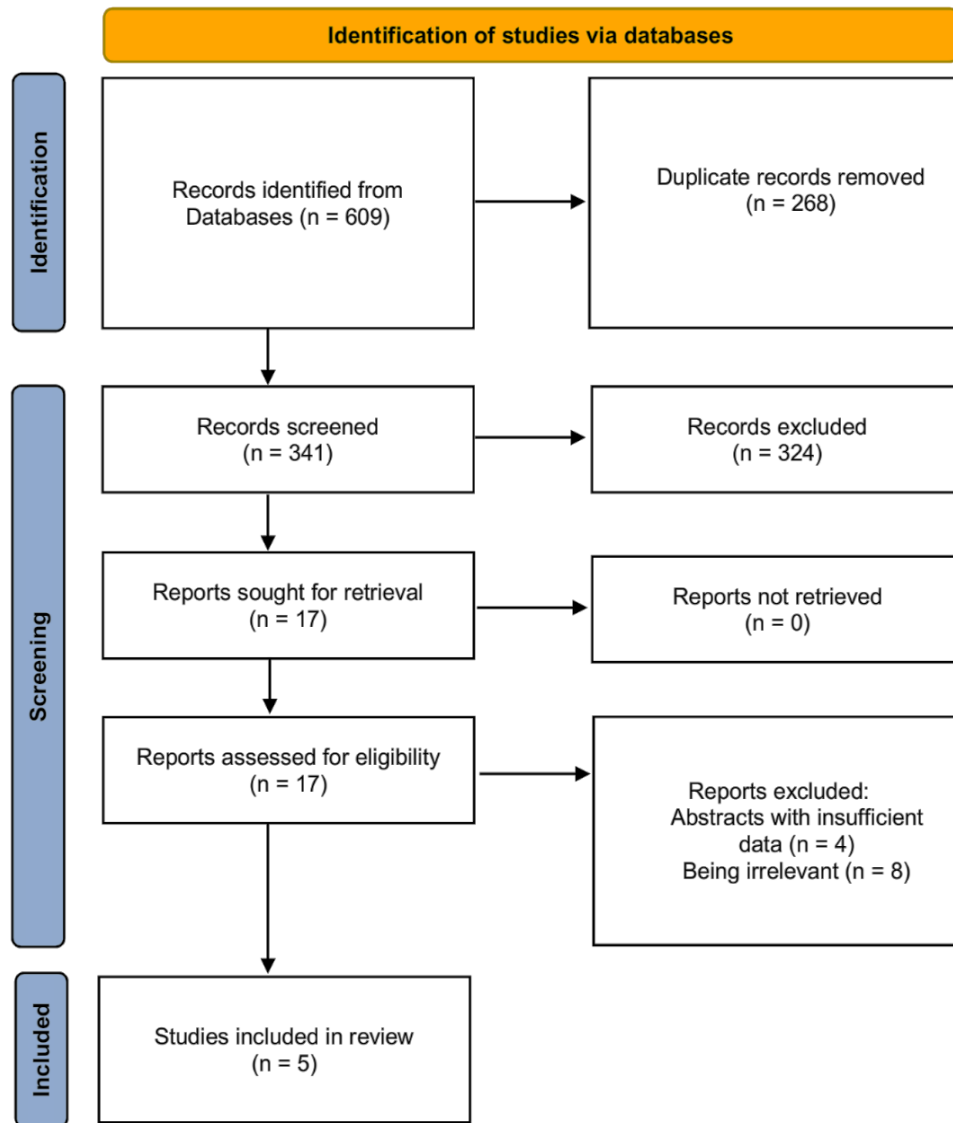


Figure 1. Flowchart and Process for Identifying, Screening, and Evaluating the Eligibility of Studies on Neurofeedback Treatment Protocols for Patients with Personality Disorders

As shown in Table 1, three out of five included articles were conducted in Germany (26, 28, 29). Among the studies, two utilized EEG neurofeedback protocols: one study employed only the fronto-central channel (30), while the other used different combinations of frontal electrodes with other scalp areas (27). The remaining three articles used real-time fMRI neurofeedback protocols: two studies focusing only on the amygdala (28, 29), and one study targeting the anterior insula (26). The types of studies were non-randomized, not-blinded case reports, case series, and single-arm trials. Consequently, all of the included studies carry a high risk of bias, and their findings are preliminary and inconclusive. All trials were performed on adult patients, both male and female.

As shown in Table 2, all of the studies used visual feedback in their neurofeedback protocols. For example, Paret *et al.* (29) and Zaehring *et al.* (28) asked patients to down-regulate a thermometer presented on either side of a disgusting image displayed on a monitor. The number of treatment sessions varied between 4 and 120 sessions. In most studies, the number of treatment sessions was tailored to the individual and determined based on the patient's desire to continue treatment as well as clinical evaluations. The outcome measures encompassed neuropsychological (Test of Variables of Attention and flanker task), behavioral (The Minnesota Multiphasic Personality Inventory, symptom assessment-24 questionnaire, self-reported impulsiveness, and Psychopathy Checklist: Screening Version, Levenson Self-Report Psychopathy Scale, Zanarini rating scale for borderline personality disorder, emotion-modulated startle, and Difficulties in Emotion Regulation Scale) and biological (fMRI and heart rate variability) measures.

Only two studies included in this review conducted follow-up assessments at six and 12 weeks. Studies examining EEG neurofeedback protocols applied more training sessions and reported improvements in patients' neuropsychological and behavioral functions both after treatment and at three-month follow-up. However, no biological assessments were conducted in these protocols. The EEG neurofeedback protocols were designed based on the power of slow brain waves and coherency between different channels at different frequency bands. On the other hand, studies examining fMRI neurofeedback protocols applied fewer training sessions. These trials demonstrated neurophysiological changes towards healthy states after treatment. For example, Paret *et al.* reported a shift in vmPFC-amygdala connectivity during fMRI neurofeedback based on amygdala activity toward healthy connectivity patterns (29). Behavioral symptoms of patients were also reported to be improved after fMRI neurofeedback. However, there appears to be a small to moderate effect size of these training protocols on behavioral symptoms related to personality disorders. Moreover, studies examining fMRI neurofeedback protocols did not assess patients' neuropsychological functioning as a post-treatment outcome measure.

Table 1. Study and Sample Characteristics for Included Studies on Neurofeedback Therapy for Personality Disorders

Authors (year, country)	Training protocol	Design				Diagnosis (Diagnostic criteria)	N Intervention (mean age)	Gender	Risk of Bias
		Study	Randomization	Blinding	Control				
Surmeli and Ertem (2009, Turkey)	EEG; delta/theta/alpha reduction reward, and theta/alpha/beta coherence reduction reward at different regions	Case series	No	No	No	Antisocial personality disorder (DSM-IV)	13 (19-48 years old)	9 male/4 female	High
Howard et al. (2013, UK)	EEG; FCz activity	case-report	No	No	No	Personality disorder (International Personality Disorder Examination)	1 (43 years old)	Male	High
Sitaram et al. (2014, Germany)	fMRI; Increasing BOLD response in the left anterior insula	Case-report	No	No	No	Psychopathy (PCL:SV and LSRP)	4 (31.5 ± 3.5 years old)	Not specified	High
Paret et al. (2016, Germany)	fMRI; amygdala down regulation	Single-arm trial	No	No	No	Borderline personality disorder (DSM-IV)	8 (33.6 ± 9.5 years old)	Female	High
Zaehringer et al. (2019, Germany)	fMRI; amygdala down regulation	Single-arm trial	No	No	No	Borderline personality disorder (DSM-IV)	24 (33.42 ± 11.10 years old)	Female	High

EEG = Electroencephalogram; fMRI = Functional magnetic resonance imaging; BOLD = Blood-oxygen-level-dependent; PCL:SV = Psychopathy checklist: screening version; LSRP = Levenson self-report psychopathy scale.

Table 2. Technical Characteristics, Outcome Measures and Results for Included Studies

Authors (year)	Feedback	Number of training sessions	Assessment times	Outcome measures	Main findings
Surmeli and Ertem (2009)	Visual	80-120	Before training and after every 20 training sessions	SA-45, MMPI, TOVA	12 out of 13 patients showed significant improvement after treatment based on all measures
Howard et al. (2013)	Visual	33	Before, immediately after and three months after training	Flanker task, Self-reported impulsiveness	Neuropsychological performance of the subject was considerably improved after treatment and at follow-up. Impulsivity of the subject was modestly improved after treatment and at follow up.
Sitaram et al. (2014)	Visual	Four daily feedback sessions for 1-3 days depending on subject availability	Before and after treatment	PCL:SV, LSRP, functional connectivity in the emotional network	Only one out of the four patients learned to up-regulate the BOLD response. Patients with higher PCL:SV scores were less able to raise the BOLD signal in the anterior insula. Neurofeedback increased connectivity in the emotional network in a patient.
Paret et al. (2016)	Visual	4	Before and after treatment	fMRI, DERS	Task-related right amygdala-vmPFC connectivity was changed during neurofeedback, leading to a pattern similar to that observed in healthy people. Resting-state functional connectivity showed increased amygdala connectivity with the DLPFC and decreased connectivity with other limbic areas. self-reports revealed a reduction in patients' dissociative experiences, and modest evidence was observed for improvement in emotion regulation after neurofeedback.
Zaehring et al. (2019)	Visual	4	Before, immediately after and six weeks after training	fMRI (EWMT, BMT), HRV, emotion-modulated startle, self-reported ZAN-BPD	Patients could downregulate their amygdala BOLD response with neurofeedback. There was a reduction in BPD symptoms as evaluated by the ZAN-BPD and in emotion-modulated startle to negative pictures after training.

SA-45 = Symptom assessment-45 questionnaire; MMPI = Minnesota multiphasic personality inventory; TOVA = Test of variables of attention; PCL:SV = Psychopathy checklist: screening version; LSRP = Levenson self-report psychopathy scale; fMRI = Functional magnetic resonance imaging; DERS = Difficulties in emotion regulation scale; EWMT = Emotional working memory task; BMT = Backward masking task; HRV = Heart rate variability; ZAN-BPD = Zanarini rating scale for borderline personality disorder; BOLD = Blood-oxygen-level-dependent; vmPFC = Ventromedial prefrontal cortex; DLPFC = Dorsolateral prefrontal cortex.

Discussion

To our knowledge, this work is the first systematic review of neurofeedback methods for the treatment of personality disorders. In general, our findings indicate that long-term, individualized training of neurofeedback treatment may be effective in reducing behavioral and neuropsychological symptoms of personality disorders. However, it should be noted that the clinical effect of neurofeedback can be relatively due to various non-specific parameters. These include the positive expectations of the patient, the rewarding experience of positive feedback, as well as regression to the mean, all of which probably contribute to the improvements observed in the group (24). It is worth noting that the latter point is irrelevant to the studies reviewed here because none of them included a control condition and were mostly based on case reports. In addition, there is great heterogeneity among the original studies in terms of the type of training protocols, study designs, assessment methods, and outcome measures. This heterogeneity makes it very difficult to reach a definitive conclusion about the effectiveness of neurofeedback for personality disorders. Furthermore, it should be noted that the number of clinical trials in this regard is very limited and much more research is needed in the future.

Both fMRI and EEG-based protocols were employed to investigate the effects of neurofeedback training on personality disorders. Each protocol has its own advantages and disadvantages for this real-time experiment. fMRI protocols, for instance, provide good spatial resolution to target subcortical and cortical regions with high precision, which can include the circuit of interest (31, 32). In contrast, EEG has excellent temporal resolution and is much less costly compared to neuroimaging modalities such as fMRI (33-35). In addition, wireless EEG systems offer new solutions for portable neurofeedback methods in the future (36, 37). Future studies can take advantage of both modalities and combine them to achieve better self-regulatory performance in patients.

fMRI neurofeedback protocols mainly target the amygdala to reduce its hyper-reactivity to emotional cues in patients with personality disorders. It is assumed that emotional instability observed in personality disorders stems from the high reactivity of the neural circuits involved in creating an emotional state with a serious defect in emotion regulation (38, 39). Amygdala hyperactivity is thought to be an abnormality in top-down control of the frontal region and thus may contribute to emotional instability (8, 40, 41). Therefore, amygdala neurofeedback therapy may be effective for regulating neural mechanisms of emotional instability in personality disorders. However, further studies are needed to confirm this hypothesis. In addition to the amygdala, a brain network including the anterior cingulate gyrus, insula, and orbitofrontal cortex is supposed to play a role in emotional state regulation (42, 43). Some studies suggest that the role of insula in emotion regulation may be

relatively overlooked in research compared to the amygdala (44). Nonetheless, insula activity is critical for various types of emotional processing (45), and patients with personality disorders receive noticeably decreased representation of the conditioned stimuli from insula-amygdala interconnections (46). Additionally, the insula has been shown to play an essential role in psychotic behaviors, with reduced gray matter volume in the mid-anterior insula being associated with personality disorder symptoms (47). Accordingly, in a pilot study, Sitaram *et al.* designed a neurofeedback training protocol based on insula function for patients with antisocial personality disorder (26). However, due to the small number of treatment sessions and the lack of personalization of the treatment, acceptable results were not obtained. Therefore, future well-designed studies should prioritize insula activity in designing their treatment protocols.

Scientific gaps and future directions

To start with, it should be clearly noted that no original study was performed with a control group. Therefore, the risk of bias in all the included articles was considerable, indicating the need for improving the quality of research in this field. Similar to other treatments, developing a neurofeedback protocol for a clinical condition requires several steps. Single-arm trials without a control group are only suitable for evaluating acceptability and feasibility issues at an early stage. Indeed, these trials provide a proof of concept for future research. However, these types of trials cannot assess the specific outcomes of neurofeedback, and non-specific effects influence the neurofeedback results of such trials (48). This is while neurofeedback methods allow the implementation of various sham conditions as passive or active controls (49). Therefore, there is a need to go one step further and design and conduct randomized controlled trials to more accurately investigate the effects of neurofeedback on personality disorders. Furthermore, some serious flaws were observed in the design of the included studies. Notably, all studies lacked sufficient statistical power. Given the growing availability of reliable and relatively inexpensive psychophysiological systems, it is entirely feasible to enroll larger sample sizes in future research. This is a significant step to identify which neurofeedback protocol is the most effective intervention for improving personality disorder symptoms.

To provide valid clinical evidence and to permit comparisons between trials while estimating a pooled effect size, we strongly recommend that future neurofeedback studies on personality disorders adopt standardized and formal approaches for the diagnosis and evaluation of symptoms and performance in patients. Moreover, given the heterogeneous etiology for developing personality disorders among patients, a more completely phenotypic and clinical characterization may aid in determining subgroups of patients who benefit more from neurofeedback treatment. In addition, it is worth noting that the current evidence in this field has been restricted to trials conducted in adult patients with

personality disorders. Thus, considering the low risk and noninvasive therapeutic protocols in neurofeedback training, we suggest that this treatment can also be investigated in younger individuals diagnosed with personality disorders.

As mentioned, the personalization of interventions plays a pivotal role in the success of neurofeedback training for personality disorders. Tailoring feedback, characteristics, and mental strategies to the unique attributes of each patient can make neurofeedback intervention more suitable for personality disorders. Additionally, machine learning methods can help the process of personalizing neurofeedback protocols (50). In fact, the complexity of neurophysiological patterns in neurofeedback demonstrates the usefulness of using statistical and artificial intelligence approaches that can help determine individual neural patterns (51). In addition, neurofeedback has great potential for integration with various technologies (52). New design and engineering advances can contribute to multimodal neurofeedback systems, incorporating a variety of visual, tactile, and auditory feedbacks to foster active engagement in treatment sessions, especially for patients with personality disorders.

Limitation

The main limitation of this work results from the small number of original articles and the high heterogeneity of the instruments used in these studies to evaluate the effects of neurofeedback on the symptoms of personality disorders. Consequently, conducting a meta-analysis was made impossible.

Conclusion

Neurofeedback is a noninvasive and complex intervention that attempts to target affective and cognitive deficits in patients with personality disorders via mental imagery-related self-regulation of relevant brain networks and regions. Individualized long-term EEG protocols have shown to be effective in ameliorating clinical, affective, and neurophysiological symptoms following neurofeedback training in patients with personality disorders. However, fMRI-based protocols have been examined in a very limited experimental condition with serious methodological problems, making it difficult to draw a correct conclusion about the efficacy of these types of neurofeedback protocols for treating personality disorders. In general, neurofeedback studies investigating this therapeutic technique for personality disorders are very preliminary and strict conclusions cannot be made at this point. Therefore, further basic and clinical investigations are required to address several open methodological and technical questions, raise consensus, and foster standardization, eventually paving the way for translational works.

Conflict of Interest

None.

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