

## Review article

## Review of EEG-based neurofeedback as a therapeutic intervention to treat depression



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## ABSTRACT

Depression, or major depressive disorder, is a common mental disorder that affects individuals' behavior, mood, and physical health, and its prevalence has increased during the lockdowns implemented to curb the COVID-19 pandemic. There is an urgent need to update the treatment recommendations for mental disorders during such crises. Conventional interventions to treat depression include long-term pharmacotherapy and cognitive behavioral therapy. Electroencephalogram-neurofeedback (EEG-NF) training has been suggested as a non-invasive option to treat depression with minimal side effects. In this systematic review, we summarize the recent literature on EEG-NF training for treating depression. The 12 studies included in our final sample reported that despite several issues related to EEG-NF practices, patients with depression showed significant cognitive, clinical, and neural improvements following EEG-NF training. Given its low cost and the low risk of side effects due to its non-invasive nature, we suggest that EEG-NF is worth exploring as an augmented tool for patients who already receive standard medications but remain symptomatic, and that EEG-NF training may be an effective intervention tool that can be utilized as a supplementary treatment for depression. We conclude by providing some suggestions related to experimental designs and standards to improve current EEG-NF training practices for treating depression.

## 1. Introduction

The current catastrophic global situation caused by the coronavirus disease 2019 (COVID-19) pandemic has led to great disruptions in people's daily lives. The pandemic has affected many people's socio-economic and mental statuses, leading to various psychological issues such as post-traumatic stress disorder, suicidal tendencies, anxiety, and depression. Depression, or major depressive disorder (MDD), is a common yet serious psychological illness that negatively affects the way a person feels, thinks, and acts. Depression affects over 120 million people worldwide, and epidemiological studies have estimated the prevalence

of depression to be around 10% to 15% in the general population. In 2001, the World Health Organization (WHO) predicted that by 2020, depression would rank second in the global disease burden and would be one of the priority mental diseases covered by the WHO's Mental Health Gap Action Programme (Sayers, 2001). Recent meta-analytic studies have demonstrated the prevalence of depression worldwide. Its prevalence in Europe and the US has been reported to range between 11.9% and 17%, with a similarly high rate in Asia (16.7%) and the lowest rates in Australia and Africa (7.3% to 11.5%), from 1994 to 2004 (Lim et al., 2018). Another meta-analysis showed the prevalence of depression to be higher in high-income countries (5.5% to 14.6%) than in low-income

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countries (5.9% to 11.1%) (Bromet et al., 2011).

Depression symptoms include sadness, loss of interest, guilt, sleep problems, tiredness, poor concentration, and a loss of interest in day-to-day activities (Lin et al., 2021; Lu et al., 2014). More severe cases of depression can lead to an increased risk of death (Cuijpers and Smit, 2002) and suicide (Choo et al., 2014; Large, 2016; Lin et al., 2021). Depression is a chronic disorder that affects an individual's quality of life (Daly et al., 2010; Mayor, 2015), social and emotional functioning (Huang et al., 2019; Huang and Huang, 2019; Wong et al., 2016), and ability to work (Hirschfeld et al., 2000; Lerner and Henke, 2008; Stewart et al., 2003). Depression also affects people's social lives. People with depression show a bias during social processing and interactions, with a tendency to pay more attention to negative aspects of social information. For example, in laboratory studies, people with depression tend to show preferential attention to sad words, sad faces, and emotional words ((Gotlib et al., 2004a,b); Mogg and Bradley, 2005). People with depression are more likely to perceive the negative attributes of social interactions or to attribute negative outcomes to themselves, and less likely to feel a sense of belonging (Joiner et al., 1999). Furthermore, depressed people are likely to exert negative effects on others and to experience a sense of rejection and the loss of a sense of reward (Joiner Jr. and Katz, 1999).

Depression can be reliably diagnosed and treated with the help of physicians (Wahlbeck, 2015). Current clinical recommendations for the treatment of depression are pharmacotherapy, psychotherapy, and a combination of the two (American Psychiatric Association, 2009; National Collaborating Centre for Mental Health (UK), 2010). Pharmacology-based therapies for depression include medications such as anti-depressants and selective serotonin reuptake inhibitors. Numerous psychological therapies are considered effective treatment options, including cognitive behavioral therapy and interpersonal therapy (Churchill et al., 2001; National Collaborating Centre for Mental Health (UK) 2010). The use of neurofeedback (NF)-based interventions have been reported recently for patients with depression and/or treatment-resistant depression (Lee et al., 2019) even after they have received conventional pharmacotherapeutic methods.

In this article, we provide a brief overview of current state-of-the-art neurofeedback systems, focusing on electroencephalogram-based neurofeedback (EEG-NF), and elaborate on the various protocols used in NF studies involving patients with depressive symptoms. We then discuss how EEG-NF can be used as a psychotherapeutic intervention to treat depression. Using an example of a generalized EEG-NF system, we first describe the fundamentals of EEG and EEG-NF systems and how they have been used to date. We then explore published studies conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021) that explore EEG-NF protocols for the treatment of depression, such as alpha symmetry and high-beta down-training. To understand the role of the EEG-NF protocols in use, we examine studies that used EEG-NF to improve cognition and other conditions in depressed people. We conclude with a discussion of methodological considerations and protocols for EEG-NF and how EEG-NF can be used as an interventional tool to treat depression.

NF-based training is used to control psycho-physiological processes in the brain through the use of external feedback. NF was developed to assist brain-machine interfaces to help individuals overcome injuries, disabilities, and/or mental illnesses (Kamiya, 1971; Lubar et al., 1995; Lubar and Bahler, 1976; Mann et al., 1992; Nowlis and Kamiya, 1970; Ordikhani-Seyedlar et al., 2016; Rozelle and Budzynski, 1995; Seifert and Lubar, 1975). NF can help an individual control the function of a brain region by training a specific set of brain waves using EEGs. EEG signals are categorized into five basic frequency components that represent specific functions of the brain: (1) *delta*, the person is asleep (0.5–4 Hz); (2) *theta*, the person is in a drowsy, meditative state (4–8 Hz); (3) *alpha*, the person is attentive (8–12 Hz); (4) *beta*, the person is alert (14–30 Hz); and (5) *gamma*, the person is engaged in higher cognitive function (30–100 Hz). NF protocols are based on these

frequency components and defined as delta, theta, alpha, beta, and gamma protocols or as ratios of the frequency components, such as the alpha/theta and beta/theta ratios (Dempster, 2012). The most important component of an NF technique is the feedback provided by an audio, video, or audio-video stimulus, which regulates the participant's brain waves.

The generalized EEG-NF system depicted in Fig. 1 is the simplest and most widely used system. EEG is primarily used in NF because it is non-invasive, cost-effective, and simple to use (Gruzelier, 2014). Recent studies have shown improvements in the use of EEG-NF for various clinical and non-clinical applications (Jeunet et al., 2019; Marzbani et al., 2016; Omejc et al., 2019). EEG-NF has been applied in the treatment of diseases such as epilepsy (Morales-Quezada et al., 2019; Nigro, 2019; Serman et al., 1974; Tan et al., 2009; Walker and Kozlowski, 2005), ADHD (Chabot et al., 2001), autism (Karimi et al., 2011), schizophrenia (Gandara et al., 2020; McCarthy-Jones, 2012; Nan et al., 2012; Pazoiki et al., 2019; Singh et al., 2020; Surmeli et al., 2012), insomnia (Hammer et al., 2011), anxiety (Blaskovits et al., 2017; Gadea et al., 2020; Patel et al., 2020; Tolin et al., 2020; Wang et al., 2019), and drug and alcohol addiction (Dalkner et al., 2017; Ko and Park, 2018; Lackner et al., 2016), and of learning disorders such as dyslexia, dyscalculia, and dysgraphia (Bearden et al., 2003; Breteler et al., 2010; Patil et al., 2022; Nazari et al., 2012; Wang and Sourina, 2013). Studies have also shown post-NF improvements in executive function and depression symptoms (Choi, 2011; Dias and van Deusen, 2011). DeRubeis et al. (2008) concluded that the NF system showed promising treatment effects in patients with depression in recent clinical trials.

The COVID-19 pandemic has highlighted the urgent need to develop more effective mental health treatments. Mitigation strategies are needed to promote mental health awareness and treatments for mental health disorders. Additional non-pharmaceutical treatments for depression and anxiety disorders are required to avoid the side effects of pharmacotherapeutic interventions. EEG-NF is one such promising technique for treating depression. In this systematic review, we first review the literature on psychotherapeutic interventions with a focus on EEG-NF for people with depression. Then, we elaborate on the protocols used to assist or treat depression in NF studies. Lastly, we discuss how current state-of-the-art EEG-NF protocols could facilitate future research and improve global health amid the COVID-19 pandemic and future public health emergencies.

## 2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards were followed for this systematic review (Page et al., 2021).

### 2.1. Search strategy

EEG-NF studies were selected using a systematic search process. A thorough search for peer-reviewed articles published in English between 2010 and August 2020 that included the treatment of depression symptoms was conducted using the PubMed database, using the following keyword combinations: (“EEG” or “Electroencephalography” or “Neurofeedback”) and (“Depression” or “Major Depressive Disorder” or “Treatment-Resistant Depression”).

### 2.2. Inclusion criteria

Independent searches and screening were conducted to ensure that the inclusion criteria were met. Studies were only included if they utilized neurofeedback (NF) based on electroencephalogram (EEG) studies as an intervention to treat participants with depression symptoms. We did not review or include studies using other modalities, such as functional magnetic resonance imaging (fMRI) or magneto-electrography (MEG). Furthermore, the studies were screened to ensure that they met

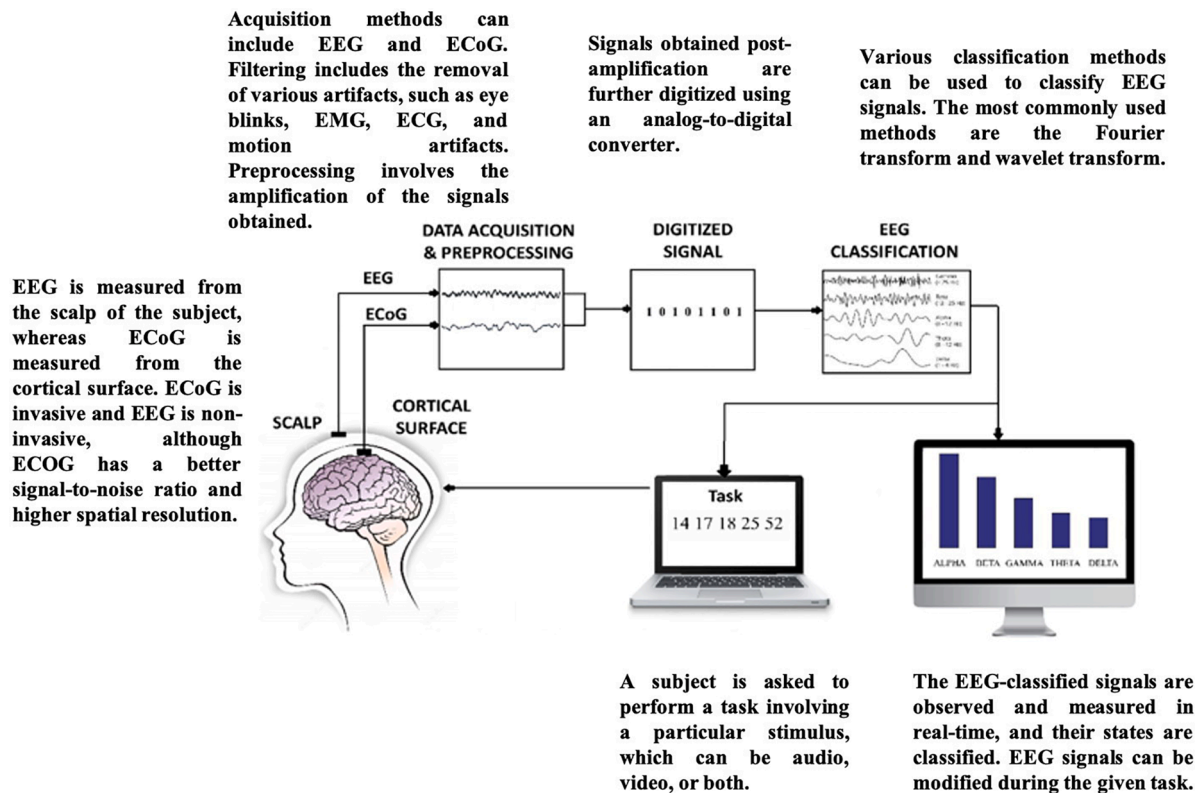


Fig. 1. Summary of components of a generalized neurofeedback system.

the following criteria: (1) were clinical or randomized empirical trials; (2) involved depression, MDD, or treatment-resistant depression; (3) included participants older than 18 years; (4) involved EEG-NF; and (5) were published between 2010 and 2020 in English. After conducting literature searches, we eliminated duplicate records and excluded theoretical papers and reviews.

### 3. Results

Among the 130 original reports discovered through the database searches, we evaluated 72 full texts for eligibility. Studies were excluded if the subjects did not fit our predetermined inclusion criteria or the researchers did not provide adequate EEG-specific findings. Finally, 12 published studies were included in the current systematic review (Fig. 2).

The 12 studies were divided into two groups based on the two NF protocols most commonly used to treat depression symptoms: (1) alpha-asymmetry (ALAY) and (2) high-beta down-training NF protocols. Other protocols used in the research to treat depression symptoms are discussed in following sections.

#### 3.1. Alpha-asymmetry (ALAY) NF protocol for treating depression

The theory of frontal alpha asymmetry was proposed by Richard Davidson (1992) as a useful neurophysiological method to treat the symptoms of depression (Davidson, 1992). The frontal ALAY method involves the identification of differences in alpha activity between the left and right frontal hemispheres during an EEG session. As indicated by Stewart et al. (2011), the left frontal hemisphere involves the behavioral activation system, which is associated with positive emotion and motivation, and the right hemisphere involves the behavioral inhibition activation system, which is associated with negative emotions, anxiety, and depression (Matherstul et al., 2008; Stewart et al., 2011; Thibodeau et al., 2006). Alpha asymmetry is indicated by a score and is abbreviated

as  $A_1$ . It is a potential marker of frontal ALAY (Baehr et al., 1997) and is usually calculated by the formula,

$$A_1 \text{ score} = \log F4 - \log F3, \quad (1)$$

where  $\log F4$  and  $\log F3$  represent the powers of the left and right frontal alpha components, respectively. The  $A_1$  score is an important indicator in resting and task-based studies involving participants with depression (Kaiser et al., 2018; Smith et al., 2017; Stewart et al., 2011). Baehr et al. (1997) defined an ALAY-NF protocol that was used to elevate the  $A_1$  score and reduce depression symptoms. A number of ALAY-based NF studies have shown reductions in symptoms related to depression over both short-term (Baehr et al., 1997; Choi, 2011; Dias and van Deusen, 2011; Mennella et al., 2017; Rosenfeld, 2000; Wang et al., 2019) and long-term (Baehr et al., 2001) follow-ups.

A pilot study by Choi et al. (2011) showed improvements in a variety of neurocognitive functions and reductions in depression-related symptoms. The improvements in the depressive symptoms of participants using the ALAY-NF protocol were assessed in clinical interviews. The 23 participants were randomly assigned to either an NF training group ( $n = 23$ ; age =  $28.46 \pm 9.69$  years; 10 females) or a placebo group ( $N = 11$ ; age =  $28.54 \pm 6.84$  years; 7 females). The NF group received the ALAY-NF protocol for about 30 min per session over a 5-week period. The placebo group participants received placebo psychotherapy training consisting of psychological assessments, interpretation of and information about test results, and treatment of mood disorders. The NF group showed significantly improved scores on the Beck Depression Inventory (BDI-II), Hamilton Rating Scale for Depression (HAM-D), and Automatic Thoughts Questionnaire-Negative (ATQ-N) compared with the placebo group. The  $A_1$  score also improved significantly in the NF group compared with the placebo group in both the eyes-open and eyes-closed conditions. The study showed that EEG-NF based on ALAY theory was associated with a reduction in depressive symptoms.

Mennella et al. (2017) reported results similar to those of Choi et al. (2011) in a sample of 32 healthy women. The participants were

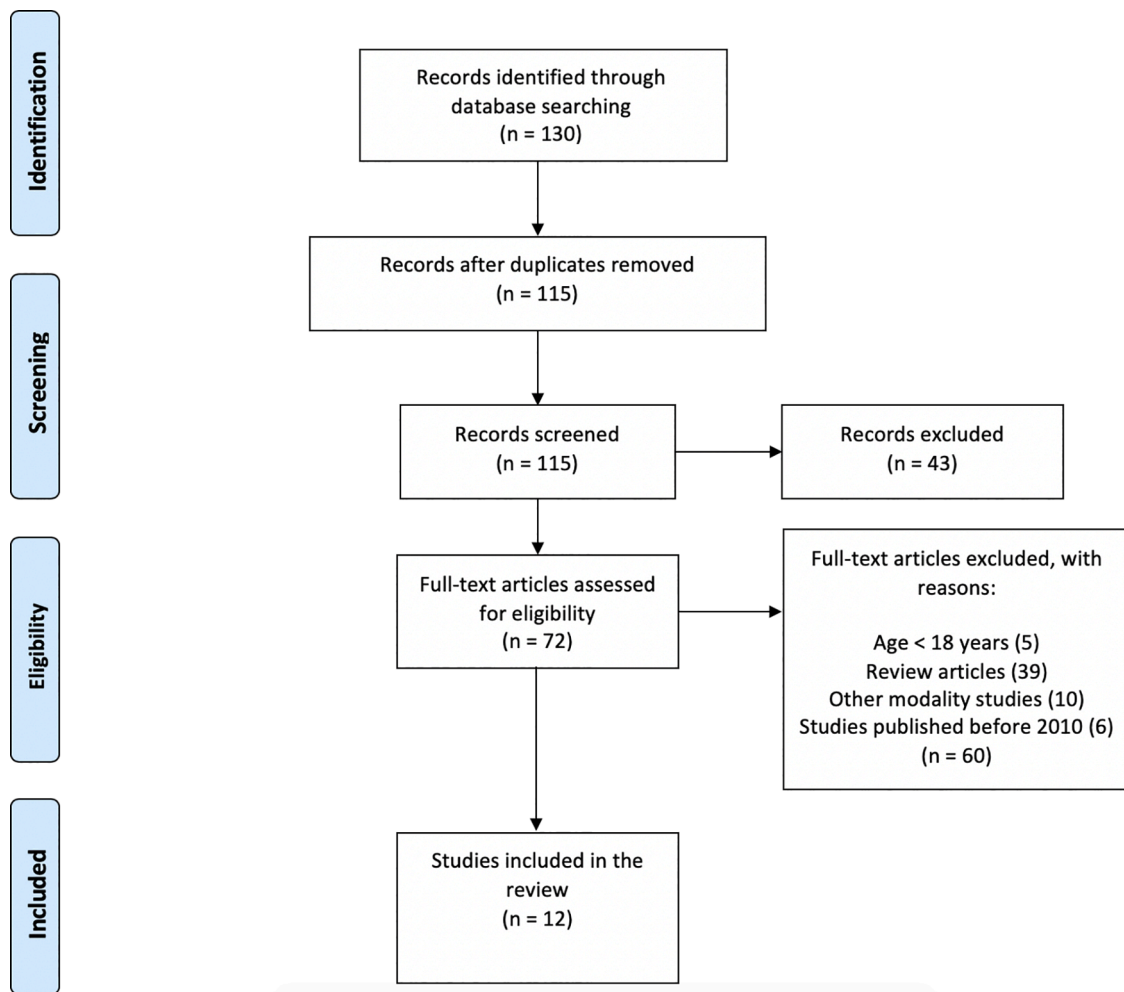


Fig. 2. The preferred reporting items for systematic review and meta-analysis (PRISMA) flow diagram for selected studies involving EEG-NF to treat depression.

randomly allocated to either an ALAY-NF ( $N = 16$ ; age =  $22.9 \pm 1.2$  years) or an active control ( $N = 16$ ; age =  $23.3 \pm 1.2$  years) group. Both groups received seven mid-frontal alpha activity NF sessions with a duration of 45 min over 2 weeks. The Beck Anxiety Inventory (BAI) and Positive and Negative Affect Scales (PANAS) were applied to both groups before and after the EEG-NF training. The participants in the ALAY-NF group scored significantly lower on the behavioral scales of the BAI and the PANAS Negative effect scores compared with the active control group from before to after NF training. The study also examined the alpha power in both hemispheres and found increased left alpha power in the ALAY-NF group compared with the controls, which increased the  $A_1$  score in the ALAY-NF group. The study further provided a rationale for using the EEG-NF-based frontal alpha asymmetry protocol as a clinical application to treat or improve symptoms related to depression. [Table 1](#)

A number of contrasting studies based on ALAY-NF have shown a reduction in the asymmetry score, with an overall reduction in depressive symptoms after the EEG-NF sessions ([Cheon et al., 2016](#); [Peeters et al., 2014](#)). [Peeters et al. \(2014\)](#) administered 30 sessions of EEG-NF over 10 weeks to reduce the alpha asymmetry in participants with depression symptoms ( $N = 9$ ; age =  $46.55 \pm 11.71$  years; 4 females). They used the Quick Inventory of Depressive Symptomatology (Self-Report) to assess depression symptoms and found a significant and feasible improvement in the post-EEG-NF session scores. The study further reported a reduction in alpha asymmetry after the EEG-NF sessions compared with the baseline, although there was no significant improvement in the  $A_1$  score. The study empirically validated the ability

of EEG-NF to reduce relative frontal asymmetry. [Cheon et al. \(2016\)](#) used an 8-week ALAY-NF protocol to increase the beta power in the left frontal electrode region (F3) and reduce the alpha power in the central electrode location (Pz) in participants with depression ( $n = 20$ ; age =  $43.25 \pm 14.29$  years; 16 females). The HAM-D, BDI-II, and Hamilton Anxiety Rating Scale (HAM-A) were used to assess depression-related symptoms. The scores on the HAM-D, HAM-A, and BDI-II were significantly reduced after the ALAY-NF sessions. However, there was no significant improvement in the  $A_1$  score. This was an ideal study for understanding the clinical application of EEG-NF in alleviating the symptoms of depression and anxiety in a small sample.

### 3.2. High-beta down-training NF protocol for treating depression

The EEG beta band (14 Hz–30 Hz) can be divided into two types of beta activity: (1) low/slow beta (12 Hz–15 Hz) activity, indicating a state of concentration and alertness, and (2) high/fast beta (22 Hz–38 Hz) activity, indicating a state of anxiety and stress ([Collura, 2014](#); [Hoffmann, 2005](#)). The high-beta reduction protocol, also called the high-beta down-training EEG-NF protocol, was developed to reduce arousal and manage anxiety, stress, and rumination ([Collura, 2014](#)). Various applications of this protocol have been used to improve stress management in athletes ([Dupee and Werthner, 2011](#)), people with post-traumatic stress disorder ([Walker, 2009](#)), and children with autism ([Thompson et al., 2010](#)).

[Wang et al. \(2019\)](#) compared the effects of ALAY-NF and high-beta down-training NF in 70 participants with depression. The participants



**Table 1**  
Summary of studies based on EEG-NF using the ALAY protocol for treating depression.

Authors (year)	Protocol	Sample Characteristics (% female)	Groups (if any)	Electrodes Used for NF	Session Details	Depression Assessments	Behavioral Results	EEG-wave Results
Choi (2011)	↑ Frontal alpha asymmetry	<b>N = 23</b> Depressive mood (74%)	<b>NF group</b> ( <i>N</i> = 12; age = 28.46 ± 9.69 years) <b>Placebo group</b> ( <i>N</i> = 11; age = 28.54 ± 6.84 years)	Alpha training: <b>F3, F4</b> referenced at Cz	10 sessions over 5 weeks; each session = 30 mins	HAM-D BDI-II ATQ-P ATQ-N DSS	BDI-II, ATQ-N, and HAM-D; a trend toward a significant reduction in scores was observed	Alpha power difference between pre- and post-tests found in the NF group
Peeters et al. (2014)	↓ Alpha asymmetry (AA)	<b>N = 9</b> MDD age = 46.55 ± 11.71 years (44%)	N/A	<b>F3, F4</b>	Maximum 30 sessions over 10 weeks; each session = 33 mins	QIDS- SR	During NF, QIDS-SR decreased significantly	Mean baseline AA decreased significantly over the sessions
Mennella et al. (2017)	Frontal alpha symmetry ; ↑ Mid-frontal alpha	<b>N = 32</b> Healthy (100%)	<b>Asymmetry group</b> ( <i>N</i> = 16; age = 22.9 ± 1.2 years) <b>Control group</b> ( <i>N</i> = 16; age = 23.3 ± 1.2 years)	Alpha asymmetry training: <b>F3-F4</b> ; Mid-frontal training: <b>Fz</b>	7 sessions over 2 weeks; each session = 45 mins	PANAS BAI BDI-II	Significant decreases in PANAS negative affect and BAI scores	Significant increase in alpha power at F4 (right) in alpha asymmetry group; no significant increase in control group
Cheon et al. (2016)	↑ Beta; ↑ theta/ ↓ alpha	<b>N = 20</b> MDD age = 43.25 ± 14.29 years (80%)	N/A	Beta training: <b>F3</b> ; Alpha/theta training: <b>Pz</b>	16–24 sessions over 8 weeks; each session = 30 mins	HAM-D; HAM-A BDI-II BAI	Mean HAM-D, HAM-A and BDI-II scores improved significantly	No significant differences in A <sub>1</sub> scores post-NF sessions

**Note:** MDD: major depressive disorder; NF: neurofeedback training; F3: left frontal electrode; F4: right frontal electrode; Cz: middle central electrode; Pz: middle parietal electrode; A<sub>1</sub>: alpha asymmetry score; HAM-D: Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; BDI-II: Beck Depression Inventory; BAI: Beck Anxiety Inventory; ATQ-P: Positive Automatic Thoughts Questionnaire; ATQ-N: Negative Automatic Thoughts Questionnaire; DSS: Depression Stigma Scale; QIDS-SR: Quick Inventory of Depressive Symptomatology–Self-report; PANAS: Positive and Negative Affect Schedule; AA: alpha asymmetry.

were divided into three groups: an ALAY-NF group (*N* = 24; age = 33 ± 14.741 years; 19 females), a high-beta down-training NF group (*N* = 23; age = 42.83 ± 15.816 years; 12 females), and a control group (*N* = 23; age = 42.61 ± 13.937 years; 16 females). The ALAY-NF and high-beta

NF groups received 10 sessions of EEG-NF training over 5 weeks, while the control group received no training. The ALAY and high-beta NF groups showed significant reductions in depression-related symptoms and a slight deviation in the A<sub>1</sub> score. Compared with the ALAY-NF

**Table 2**  
Summary of studies based on EEG-NF using the high-beta down-training protocol for treating depression.

Authors (year)	Protocol	Sample Characteristics (% female)	Groups (if any)	Electrodes Used for NFT	Session Details	Depression Assessments	Behavioral Results	EEG-wave Results
Wang et al. (2019)	Alpha asymmetry (↑ A1 score); ↓ High-beta	<b>N = 70</b> MDD (59%)	<b>ALAY group</b> ( <i>N</i> = 24; age = 33 ± 14.741 years) <b>High-beta group</b> ( <i>N</i> = 23; age = 42.83 ± 15.816 years) <b>Control group</b> ( <i>N</i> = 23; age = 42.61 ± 13.937 years)	ALAY training: <b>F3, F4</b> High-beta down-training: <b>P3, P4</b>	10 sessions over 5 weeks	BDI-II BAI	Improvements in BDI-II and BAI found in the ALAY and high-beta group	Significant decreases in P3 and P4 electrode high-beta in beta group, whereas control showed increased beta at P3 and P4
Chen & Lin (2020)	↓ High beta	<b>N = 23</b> MDD and anxiety age = 43.17 ± 15.82 years (52%)	N/A	<b>P3, P4</b>	10 sessions over 5 weeks; each session = 60 mins	BDI-II BAI	Significant decrease in BDI-II and BAI scores post-NF sessions	Significant decrease in low and high beta at P3 and P4 post-NF sessions

**Note:** F3: left frontal electrode; NF: neurofeedback training; MDD: major depressive disorder; ALAY: Alpha-asymmetry neurofeedback protocol; Fz: middle frontal electrode; F4: right frontal electrode; Cz: middle central electrode; P3: left parietal electrode; P4: right parietal electrode; A<sub>1</sub>: alpha asymmetry score; BDI-II: Beck Depression Inventory; BAI: Beck Anxiety Inventory.

group, the high-beta NF group showed greater reductions in beta power and in depression and anxiety symptoms. A recent study by [Chen and Lin \(2020\)](#) examined the effect of high-beta down-training on participants with depression or depression symptoms ( $N = 23$ ; age =  $43.17 \pm 15.82$  years; 12 females). The participants received 10 sessions of high-beta down-training over 5 weeks. Depression and symptoms related to depression were assessed using the BDI-II and BAI, and the participants' scores were significantly reduced after the training. The study also reported significant reductions in low- and high-beta activity over both hemispheres. [Table 2](#) lists the studies based on EEG-NF using the high-beta down-training protocol for treating depression.

### 3.3. Other EEG-NF protocols used in depression-based studies

Studies using EEG-NF to alleviate depression and its symptoms have also shown improvements in other areas of cognition. A number of studies have also shown the alleviation of various conditions that are directly or indirectly related to depression. These studies are discussed in the following section.

### 3.4. EEG-NF to improve cognition

[Lee et al. \(2019\)](#) used two EEG-NF protocols and assessed the serum concentrations of brain-derived neurotrophic factor (BDNF) in patients with treatment-resistant depression (TRD) and healthy controls. The TRD patients were divided into two groups. Over a 12-week period, the EEG-NF augmentation group ( $N = 12$ ; age =  $48.25 \pm 14.44$  years; 9 females) received 12–24 sessions of training using the elevation of the sensorimotor rhythm (SMR)/beta for 30 min, followed by training using the theta/alpha protocol for 30 min. This group received combined EEG-NF training and medication treatment. The treatment as usual (TAU) group ( $N = 12$ ; age =  $54.33 \pm 12.67$  years; 8 females) received medication and psychotherapy placebo treatment sessions instead of EEG-NF training. Patients in the TRD groups and healthy controls provided blood samples for BDNF assessment at baseline. HAM-D and BDI-II depression scores were assessed in the TRD groups. The results showed significant decreases in the HAM-D and BDI-II scores in the EEG-NF group compared with the TAU group. Compared with the TAU group, the EEG-NF augmentation group also saw significant reductions in the quality of life and functional recovery scores measured using the Sheehan Disability Scale (SDS) and the 5-level version of the European Quality of Life Questionnaire 5-Dimensional Classification (EQ-5D-5 L) scores. However, the study did not find a significant difference in the baseline serum BDNF concentrations between the three groups.

Several studies have incorporated EEG-NF protocols such as the upper-alpha protocol and peak-alpha protocol to examine cognitive performance in participants with depression symptoms. [Escolano et al. \(2014\)](#) used EEG-NF and compared improvements in working memory performance in 74 participants with depression, divided into the NF group ( $N = 40$ ; age =  $53.7 \pm 10.87$  years; 25 females) and the control group ( $N = 20$ ; age =  $49.5 \pm 10.18$  years; 16 females). Both groups received the increasing upper alpha protocol over the parieto-occipital region over a 5-week period. The participants with depression showed improvements in working memory performance, especially processing speed and performance, compared with the control participants. The Patient Health Questionnaire (PHQ-9) was used to assess depression and its severity, and there was a significant decrease in scores after the EEG-NF sessions. The study further observed a significant increase in the upper peak alpha power across participants with depression, both during rest and during task performance. This study thus indicates that the upper-alpha EEG-NF protocol can be used to improve working memory and alleviate depression symptoms.

### 3.5. EEG-NF improves other conditions associated with depression

A number of studies have used EEG-NF-based protocols, including

SMR/beta and alpha/theta, to improve not only symptoms of depression but also associated conditions ([Table 3](#)). [Kayiran et al. \(2010\)](#) used an EEG-NF-based increasing SMR/theta protocol to alleviate anxiety and depression symptoms in 36 participants with fibromyalgia syndrome. The participants were randomly assigned to two groups: a medication plus NF group ( $N = 18$ ; age =  $31.78 \pm 6.17$  years) and a control group ( $N = 18$ ;  $32.39 \pm 6.72$  years). The NF group received the EEG-NF treatment and medication, whereas the control group received medication only. The NF group was trained to elevate SMR and reduce theta for about 30 min per session, with 5 sessions per week for 4 weeks, whereas the patients in the control group received medication for 8 weeks. The NF group showed significantly reduced depression scores compared with the control group. There was also a significant decrease in the theta/SMR ratio in the fourth week of training, indicating the potential clinical use of the protocol.

[Choobfroushzadeh et al. \(2015\)](#) used EEG-NF to alleviate depression and fatigue symptoms in 24 participants with multiple sclerosis. The participants were randomly assigned to two groups: an EEG-NF group ( $N = 12$ ; age =  $34.28 \pm 8.17$  years; 6 females) and a TAU group ( $N = 12$ ; age =  $33.39 \pm 7.72$  years; 6 females). The study protocol aimed to elevate beta and reduce alpha and theta during 16 30-minute sessions over 8 weeks. Scores on the Hospital Anxiety and Depression Scale and Fatigue Severity Scale showed significant decreases in the NF group compared with the TAU group. The effects were maintained at a 2-month follow-up, indicating that EEG-NF may have long-term effects and be successful in clinical applications.

A similar EEG-NF study by [Lackner et al. \(2016\)](#) used a simultaneous theta and alpha increase protocol in 25 participants with alcohol use disorder and symptoms related to depression. The participants were randomly assigned to two groups: an EEG-NF group ( $N = 13$ ; age =  $38.9 \pm 9.1$  years) and a control group ( $N = 12$ ; age =  $40.5 \pm 8.8$  years). The NF group received the EEG-NF training sessions, whereas the control group received TAU. The NF group was trained to elevate alpha and theta simultaneously for 20 min per session over 6 weeks. The study reported significant improvements in depression symptoms and anxiety measured by the BDI-V, Posttraumatic Growth Inventory, and Brief Symptom Inventory (BSI) in the EEG-NF group compared with the control group. The EEG-NF group also showed significant improvements in theta and alpha amplitudes compared with the control group.

[Yu et al. \(2020\)](#) compared the effect of increasing peak alpha in participants with dysphoria who were randomly assigned to an EEG-NF group ( $N = 12$ ; age =  $22.33 \pm 2.43$  years; 8 females) and a sham-control group ( $N = 12$ ; age =  $23.05 \pm 3.25$  years; 6 females). The NF group received EEG-NF peak alpha training during 20 30-minute sessions over 10 weeks, and the sham-control group received an audio signal-detecting task. The NF group showed significant reductions in rumination and depression, as measured by the BDI-II, compared with the sham-control group. The peak alpha also showed a significant increase in the NF group compared with the sham-control group, indicating improvements in working memory capacity and executive functions, as well as a reduction in depressive symptoms.

## 4. Discussion

This systematic review of studies on EEG-NF for the treatment of depression shows that the included studies produced statistically significant clinical improvements. The most important element in the design of an EEG-NF experiment is the EEG protocol. To compare the between-group clinical effects across various EEG-NF studies, we grouped the studies in this review according to the EEG protocols used.

One of the most commonly used protocols is the ALAY protocol; this is based on Davidson's model of emotion, which indicates the degree of anger associated with approach behavior and links it to the corresponding brain region (i.e., activity in the left prefrontal region) ([Davidson et al., 1990](#)). This model characterizes the potential association of emotional processing and emotional regulation with unbalanced

Table 3

Summary of studies based on EEG-NF using *other protocols* for treating cognitive functions and depression in various conditions/diseases.

Authors (year)	Protocol	Sample characteristics (% female)	Groups (if any)	Electrodes Used for NF	Session Details	Depression Assessments	Behavioral Results	EEG-wave Results
Kayiran et al., (2010)	↑SMR; ↓theta	N = 36 FMS (N/A)	<b>NF group</b> (N = 18; age = 31.78 ± 6.17 years) <b>Control group</b> (N = 18; age = 32.39 ± 6.72 years)	SMR training: C4	20 sessions over 8 weeks; each session = 30 mins	HDS BDS HAS BAS	The NF group showed significantly lower mean HDS, BDS, HAS, and BAS scores than the control group	Theta/SMR ratio showed a significant decrease at the 4th week in the NF group
Escolano et al. (2014)	↑ Upper alpha (UA)	N = 60 Healthy (68%)	<b>NF group</b> (N = 40; age = 53.7 ± 10.87 years) <b>Control group</b> (N = 20; age = 49.5 ± 10.18 years)	P3, P4, Pz, O1, and O2	8 NF sessions over 5 weeks; each session = 32 mins	BDI-II PHQ-9	No significant change in BDI-II; the mean PHQ-9 score was slightly lower in the NF group	Significant increase in UA power in rest and task-related activity in the NF group
Chooforoushadeh et al. (2015)	↓ Theta and ↓ alpha; ↑ beta	N = 24 Relapsing-remitting multiple sclerosis (50%)	<b>NF group</b> (N = 12; age = 34.28 ± 8.17 years) <b>TAU group</b> (N = 12; age = 33.39 ± 7.72 years)	F3 for NF group	16 sessions over 8 weeks; each session = 30 mins	FSS HADS	Depression scores improved between the pre- and post-tests	N/A
Lackner et al. (2016)	↑ Alpha and theta (simultaneously)	N = 25 AUD (0%)	<b>NF group</b> (N = 13; age = 38.9 ± 9.1 years) <b>Control group</b> (N = 12; age = 40.5 ± 8.8 years)	Fz (Alpha NF) Pz (Theta NF) Cz (Control)	12 sessions over 6 weeks; each session = 20 mins	BDI-V BSI FKV-I FPTM-23 PPR SOC-13	Significant improvements in the BDI-V, BSI, and PPR scores compared with control group	Increased absolute alpha and theta amplitudes post-NF compared with the control group
Lee et al. (2019)	Two NF: 1 SMR/beta ↑; 2 ↑theta/ ↓ alpha	N = 24 (TRD) & N = 12 (Healthy) (67%)	<b>NF augmentation group</b> (N = 12; age = 48.25 ± 14.44 years) <b>TAU group</b> (N = 12; age = 54.33 ± 12.67 years) <b>Healthy control group</b> (N = 12; age = 43.50 ± 13.80 years)	SMR training: T4 Beta training: F3/T3 Alpha/theta training: Pz	12–24 sessions over 12 weeks; each session = 30 mins	HAM-D BDI-II	HAM-D and BDI-II in the NF augmentation group significantly decreased over 12 weeks compared with the TAU group	N/A
Yu et al. (2020)	↑ Peak alpha	N = 26 Dysphoric (54%)	<b>NF group</b> (N = 14; age = 22.33 ± 2.43 years) <b>Sham-control group</b> (N = 12; age = 23.05 ± 3.25 years)	Peak alpha training: Fp1, Fp2	20 sessions over 10 weeks; each session = 30 mins	BDI-II	Depression and rumination significantly decreased after NF sessions	Increased peak alpha indicated enhanced executive function and reduced rumination and depression

**Note:** NF: neurofeedback training; FMS: fibromyalgia syndrome; SMR: sensorimotor rhythms; AUD: alcohol use disorder; TRD: treatment-resistant depression; TAU: treatment as usual; C4: right central electrode; P3: left parietal electrode; Pz: middle parietal electrode; O1: left occipital electrode; O2: right occipital electrode; F3: left frontal electrode; Fz: middle frontal electrode; Cz: middle central electrode; T4: right temporal electrode; T3: left temporal electrode; Fp1: left frontal pole; Fp2: right frontal pole; HDS/HAM-D: Hamilton Depression Rating Scale; BDS: Beck Depression Scale; HAS: Hamilton Anxiety Scale; BAS: Beck Anxiety Scale; BDI-II: Beck Depression Inventory; PHQ-9: Patient Health Questionnaire; FSS: Fatigue Severity Scale; HADS: Hospital Anxiety and Depression Scale; BSI: Brief Symptom Inventory; FKV-lis: Freiburg Questionnaire on Coping with Illness; FPTM-23: Therapy Motivation Questionnaire; PPR: Posttraumatic Growth Inventory; SOC-13: Sense of Coherence Scale.

neural resources in the left and right frontal cortex (Harmon-Jones et al., 2010). The model further indicates that hypoactivation in the left frontal regions of the brain is associated with depression (Henriques and Davidson, 1990, 1991) and that the alpha power is higher in the right than in the left frontal region because of hypoactivation in the left region. In the ALAY protocol, participants are trained to decrease left

frontal alpha activity and increase right frontal activity, thus increasing the A<sub>1</sub> score. However, EEG-NF studies using the ALAY protocol have received criticism (Esmail and Linden, 2011). Although the ALAY protocol has received support from a few studies, other evidence suggests that there is no specific association between increased left frontal alpha activity and depression (Bhagal et al., 2004). A few studies have been

able to modulate the A<sub>1</sub> score, whereas others have shown no modulation in participants with depression, again indicating an inconsistency in the findings of studies using the ALAY protocol.

ALAY-based EEG-NF studies have also shown smaller group differences in control conditions compared with NF groups. Although these studies have reported substantial clinical effects of EEG-NF, their sample sizes have been rather small. A recent EEG-NF study by Wang et al. (2019) compared two protocols, ALAY and high-beta down-training, in participants with depression and concluded that the high-beta down-training protocol was more effective. The efficacy of high-beta down-training was further supported by Chen and Lin (2020), who reported superior behavioral and clinical outcomes compared with ALAY in participants with depression.

Another limitation of studies on EEG-NF for treating depression is that many of them include only one group. Very few studies have compared participants with depression to a healthy control group. Hammond (2005) observed some improvement in participants with depression after three to six 30-minute NF sessions, a significant improvement after 10 to 12 sessions, and complete recovery after 20 to 22 sessions. Further, the treatment relieved not only depression but also other conditions, including anxiety and rumination, introversion, and withdrawal. Most of the studies in this review used >8 sessions of neurofeedback training, although there was some variance in the number and duration of sessions. Despite the encouraging results, controlled trials of EEG-NF for treating depression are needed.

EEG-NF training to alleviate depression symptoms is an encouraging development because it is non-invasive and has minimal side effects compared with methods such as pharmacotherapy, intense transcranial magnetic stimulation, and electroconvulsive therapy. Recent studies have suggested that EEG-NF could be a major therapeutic tool for various disorders. Despite this potential, more high-quality research is needed. It would be beneficial to develop more protocols based on bimodal or multimodal NF to improve the efficacy of the training and its role in clinical applications. It would also be helpful to incorporate EEG-NF and fMRI-NF, as the overlap between time and spatial resolution would provide insight into the effects of NF on participants with depression and facilitate the identification of suitable and predictive biomarkers of depression. Currently, the use of EEG-NF as a treatment for depression is limited, but its potential seems to be enormous.

The findings of this review support the use of EEG-based NF as an evidence-based treatment for depression. Nevertheless, the evidence is limited because NF is a complex intervention that involves various independent factors in the experimental design. These include control designs featuring variations such as the comparison of a group receiving standard medication plus EEG-NF with a control group receiving standard medication only (also referred to as a passive control design), or of a group receiving continued standard medication with EEG-NF with a group receiving continued standard medication with targeted EEG-NF (also referred to as an active control design). It was difficult to select an acceptable design for EEG-NF research (Lubianiker et al., 2019; Sorger et al., 2019), but some studies have provided compelling evidence for its efficacy (Thibault et al., 2016; Sorger et al., 2019; Ros et al., 2020). In addition to the control design, EEG-NF systems offer several benefits to the user, including individualized treatment, ease of use, and detailed user-specific EEG analysis. Future studies aiming to understand the neural mechanisms of EEG-NF and its effects on depression should use larger sample sizes, as well as longer follow-up periods to understand the efficacy and clinical effects of EEG-NF (Becerra et al., 2006; Gevensleben et al., 2010; Lubianiker et al., 2019; Mehler et al., 2018; Rance et al., 2018). The current systematic review sheds light on how EEG-NF can be utilized as a treatment for depressive symptoms. The effectiveness of EEG-NF protocols in treating depression symptoms in the general population is limited. For a deeper knowledge of the benefits of EEG-NF, further EEG-NF research that compares participants without pharmacological therapies, participants with depression, and healthy control participants are needed. Future studies also should concentrate

on EEG-based biomarkers in individuals with depression to examine how they change or remain constant with age and how they respond to EEG-NF training. EEG and fMRI treatments can be used simultaneously to better understand the impact of the neurobiology of depression throughout a lifespan. Overall, the evidence from the 12 published studies included in this systematic review suggests that more research is needed to understand the efficacy of EEG-NF research and its use in treating depression symptoms. This is the first systematic review to examine the efficacy of EEG-NF as an intervention to treat depression symptoms, and the findings indicate that EEG-NF training may be an effective intervention tool that can be utilized as a supplementary treatment for depression.

The global pandemic caused by COVID-19 has raised many concerns and disrupted the everyday lives of people around the globe (Kokou-Kpolou et al., 2020; Voitsidis et al., 2020; Wu, 2020). For most of the population, this global public health crisis has been an extremely stressful period (Qiu et al., 2020; Zhang et al., 2020) and has affected many people's mental and psychological health both directly and indirectly. Research has reported the increased prevalence of psychological problems such as anxiety disorders (Huang and Zhao, 2020), depression symptoms (Elbay et al., 2020), insomnia (Kokou-Kpolou et al., 2020; Voitsidis et al., 2020), and post-traumatic stress symptoms (Lin et al., 2020) in both developing and developed countries. Hence, there is a need to update the treatment recommendations for mental disorders during such crises. The development of EEG-NF to alleviate depression symptoms is particularly encouraging amid the current COVID-19 pandemic because it is a complex yet relatively non-invasive intervention compared with other pharmacotherapeutic interventions. EEG-NF targets both cognitive and affective processes in patients with depression. As it has minimal or no side effects, the approach has good face validity for treating depression. Patients with depression have shown significant clinical and neural improvements following EEG-NF training. Moreover, given its low cost and the low risk of side effects due to its non-invasive nature, we consider EEG-NF worth exploring as an augmented tool for patients who receive standard medications but remain symptomatic.

However, this systematic review reveals that previous studies have not always followed best practices in EEG-NF designs, and it highlights several issues that should be considered when developing such designs. Some of the major issues in many of these studies are small and unbalanced sample sizes, blinding in random control designs, and a lack of follow-up protocols. These issues increase the difficulty of evaluating the clinical effects of EEG-NF and should be addressed in future studies. We recommend that future studies include sufficient investigations, improved techniques, and controlled research trials to better understand the efficacy of EEG-NF in treating depression.

## Declaration of Competing Interest

The authors declare no competing interests.

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